A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis

Sponsor:	Medivir AB Blasieholmsgatan 2, 111 48 Stockholm, Sweden
Clinical Research Organization:	PAREXEL International (IRL) Limited, 70 Sir John Rogerson's Quay, Dublin 2, Ireland.
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Sponsor Protocol No.:	MIV-711-201
EudraCT No.:	2015-003230-26
Study Drug Name:	MIV-711
Development Phase:	Phase IIa
Date of Protocol:	20 July 2016
Date of Previous Protocols:	09 September 2015 (original) 13 January 2016 (Version 2, Amendment 1)

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki [1] and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1996 and the guidelines on GCP.

_____ _____

John Öhd, MD PhD
Director Clinical R&D
Medivir AB

Date

Declaration of the National Coordinating Investigator

Title: A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 1996 and the guidelines on GCP.

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UNITED KINGDOM

Country

Declaration of the Investigator

Title: A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form (eCRF), Patient Reported Outcomes (PRO), subject diaries and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

Signature Date

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Title (block letters)

Institution (block letters)

Country

PROTOCOL SYNOPSIS

Title	A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis
Sponsor Study No.	MIV-711-201
Phase	Phase IIa
Sponsor	Medivir AB Blasieholmsgatan 2, 111 48 Stockholm, Sweden
Principal or Global Coordinating Investigator	Prof. Philip Conaghan University of Leeds Leeds Institute of Rheumatic and Musculoskeletal Medicine Chapel Allerton Hospital Chapeltown Road Leeds LS7 4SA, United Kingdom
Study Centers	Six sites distributed in 6 European countries. 1) University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, United Kingdom 2) PAREXEL Berlin Early Phase Clinical Unit, PAREXEL International GmbH, Spandauer Damm 130, 14050 Berlin, Germany 3) MC Comac Medical, 13 Urvich Str, 1612 Sofia, Bulgaria 4) LLC ARENSIA Exploratory Medicine, Research Institute of Clinical Medicine, 13a, Tevdore Mgvdeli Str. 0112 Tbilisi, Georgia 5) LLC ARENSIA Exploratory Medicine, Republican Clinical Hospital, 29 Testemitanu Str. 2025 Chisinau, Republic of Moldova 6) SC ARENSIA Exploratory Medicine SRL Colentina Clinical Hospital, Spitalul Clinic Colentina Pavilion K, etaj III Sos. Stefan cel Mare Nr. 19-21, Sector 2 Bucharest 020125, Romania
Objective	To assess the effect of MIV-711 on knee pain (week 26), as measured by an 11-point numerical rating scale in patients with symptomatic and radiographic knee osteoarthritis

Design

This is a multicentre, randomised, placebo-controlled, double-blind, three-arm parallel, Phase IIa study to evaluate the efficacy, safety and tolerability of MIV-711 in patients with symptomatic and radiographic knee osteoarthritis (OA).

A total of 240 patients with knee OA meeting the eligibility criteria and who provide written informed consent will be randomised on a 1:1:1 basis to the intervention (MIV-711 low dose 100 mg or high dose 200 mg) or placebo.

Patients who are eligible and agree to continue with the study will return for the baseline visit within 30 days of the screening visit.

After baseline assessments have been completed, patients will be randomised in a 1:1:1 ratio via a central secure 24-hour randomisation service to the intervention (MIV-711) arms or the placebo-controlled arm. The study will include 26 weeks of treatment, with patients followed for a total of 30 weeks as per Study procedure. Study visits for clinical assessment and questionnaires will occur at visit 2 (baseline) and visit 5 and at visit 6 and visit 8, regardless of treatment group. Patients will have a magnetic resonance imaging (MRI) of the target knee at visit 2 (baseline) and visit 8.

Main study visits for efficacy and safety will occur at visit 2 (baseline), visit 5, visit 6 and visit 8. At these visits, patients will undergo a full physical examination (target examination only at visit 3, visit 4 and visit 7) and vital signs will be recorded. Full haematology and biochemistry panels, parathyroid hormone and urinalysis will be performed at all visits. Additional biological sub study samples (blood/urine) will be taken at these visits for assessment of the biomarker response to MIV-711. Knee MRI (of the worst/target knee) will be undertaken at visit 2 (baseline) and visit 8. Patient-reported outcomes will be recorded at visit 2 (baseline), visit 5, visit 6 and visit 8. First dose will be initiated following completion of all baseline assessments and following randomisation.

Additional clinic visits for safety will be conducted at visit 3 and visit 4 and at visit 7 and visit 9. At these visits, patients will undergo a targeted physical examination, vital signs will be recorded, clinical laboratory samples assessed and an ECG conducted. Patients will be questioned about the occurrence of any adverse events since the last study visit. At the final visit 9, knee pain will be assessed using a numeric rating scale (NRS) to determine any carry-over effects of the investigational medicinal product (IMP) post-cessation of dosing. Follow-up telephone calls to assess safety and tolerability will occur 5-9 days after visit 2, visit 3, visit 4, visit 5, visit 6, and visit 7.

In addition to the normal visit schedule, unscheduled visits will be undertaken if the patient is unwell or there are any concerns as to the progress. Patient visits will be considered valid if they take place within ±2 days of the scheduled day for the visit 4 and visit 5 and within ±7 days of the scheduled day for visit 6, visit 7, visit 8, and visit 9, but will revert to the original schedule for the next visit.

Patients will be followed for 30 weeks in total, including 4 weeks after the dosing period, when final safety checks will be made.

A patient pain diary and analgesia questionnaire will be completed in an e-diary format daily during three two-week periods before visit 2 (baseline), visit 6 and visit 8.

The end of the study is defined as the last visit (visit 9, week 30) of the last patient or, if applicable, when the last patient has rolled over to study MIV-711-202 and having finalized visit 2 of that study.

Treatment	Patients will receive a once-daily 100 mg or 200 mg oral dose of MIV-711, or placebo for 26 weeks in addition to their current medication.
Number of Patients	A total of 240 patients MIV-711 100 mg: 80 patients MIV-711 200 mg: 80 patients Placebo: 80 patients
Population	The study population is defined as knee OA patients with chronic pain and Kellgren and Lawrence classification grade (K-L) ≥2 or 3.

Criteria for inclusion and exclusion

Inclusion:

1. Current average knee pain, defined as pain in either knee, within 1 week before visit 1, for which the patient gives a severity score of ≥4, <10 on a 0-10 NRS.
2. Inclusive of 40-80 years old.
3. Diagnosis of primary knee osteoarthritis, based upon the following:
   - Fulfilling the American College of Rheumatology Clinical and Radiographic (ACR) criteria for OA defined as knee pain for most days of the prior month and at least one of the following three factors: age >50 years, morning stiffness of less than 30 minutes and knee crepitus on motion.
   - X-ray evidence within the last 12 months for Kellgren and Lawrence (K-L) classification grade 2 or 3.
4. Female patients must be non-pregnant, non-lactating and of non-childbearing potential either as naturally (spontaneously) post-menopausal or due to hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy (as determined by patient medical history). Naturally (spontaneously) post-menopausal is defined as being amenorrhoic for 12 months without an alternative medical cause and with a screening follicle stimulating hormone indicating a post-menopausal state.
5. Male patients should avoid fathering a child by either of the following methods:
   - True sexual abstinence: meaning that heterosexual abstinence is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence such as that based on calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of a trial, or withdrawal/coitus interruptus are not acceptable methods of contraception).
   - Willingness to use two effective means of contraception with their partner from the time of first IMP administration until 3 months after the last dose of IMP. Two or more of the following methods are acceptable and must include at least one barrier method: i) Surgical sterilisation (i.e., bilateral tubal ligation for female partners; vasectomy for male), ii) placement of an intrauterine device or intrauterine system, iii) hormonal contraception (implantable, patch, oral), iv) barrier methods including condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Male patients who have been sterilised are required to use one barrier method of contraception (condom).
6. The patient's usual analgesic regimen (in case of use) should remain the same for 4 weeks prior to signature of the informed consent form.
7. Needs to be able to communicate well with the investigators and staff.

   Able to comply with the requirements of the study procedures and provide written informed consent prior to any study related procedures.

Exclusion:

1. The presence of any inflammatory arthritis (e.g., gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy) or any underlying condition, other than osteoarthritis, that may result in abnormal cartilage and bone metabolism.
2. Any generalised pain condition that may interfere with the evaluation of the target knee pain (e.g., fibromyalgia) as judged by the investigator.
3. A history of cancer within the previous 5 years (except for cutaneous basal-cell or squamous-cell cancer resolved by excision and cancer in situ which are allowed).
4. Ongoing or a history of atrial fibrillation.
5. Currently receiving medication that affects cartilage or bone metabolism (hormone replacement therapy taken for more than 6 months is allowed).
6. Current or recurrent disease that could affect the action, absorption or disposition of MIV-711, or could affect clinical assessments or clinical laboratory assessments.
7. Any clinically severe or significant uncontrolled concurrent illness, which, in the opinion of the Investigator, would impair ability to give informed consent or take part in or complete this clinical study.
8. Known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.
9. A positive human immunodeficiency virus (HIV) antibody screen, a positive Hepatitis B surface antigen (HBsAg) screen, and/ or a positive Hepatitis C virus (HCV) antibody screen. A positive total Hepatitis B core antibody (anti-HBc) test in conjunction with a negative antibody to Hepatitis B Surface Antigen (anti-HBs) test.
10. History of alcohol or other substance abuse within the last year.
11. Use of an investigational product within 4 weeks prior to receiving the first dose of investigational product or active enrolment in another drug or vaccine clinical study.
12. Significant target knee injury or surgery within the 6 months preceding enrolment in the study.
13. A history of partial or complete joint replacement surgery in the target knee at any time, listed for knee surgery, or anticipating knee surgery during the study period.
14. Any factor which, in the opinion of the investigator, would jeopardise the evaluation or safety of the patient or be associated with poor adherence to the clinical study protocol (e.g., inability to complete study diary, poor tolerability of venipuncture or lack of adequate venous access for required blood sampling during the study period).
15. Use of intra-articular hyaluronic acid in the target knee within the 3 months preceding enrolment in the study.
16. Use of intra-articular, intra-muscular or oral corticosteroids in the 2 months preceding enrolment.
17. Commencement of non-pharmacological OA interventions within two months preceding enrolment.
18. Vulnerable patients, e.g., patients kept in detention, soldiers, and employees of the sponsor or the contract Research Organisation (CRO) with direct involvement in the proposed study or other studies under the direction of the investigator or the CRO, as well as family members of the employees or the investigator.
19. Patients with contra-indication to MRI of the knee.

Outcome variables

Efficacy:

Primary efficacy endpoint:

- Change from visit 2 (baseline) to visit 8 in NRS average target knee pain score

Key secondary efficacy endpoint:

- Change from visit 2 (baseline) to visit 8 in knee joint MRI bone area

Secondary efficacy endpoints:

- Change from visit 2 (baseline) to visit 8 in NRS worst target knee pain score
- Change from visit 2 (baseline) to visit 8 in NRS average contralateral knee pain score
- Change from visit 2 (baseline) to visit 8 in constant and intermittent OA pain
- Change from visit 2 (baseline) to visit 8 in knee joint OA symptoms; WOMAC (function, pain, stiffness)
- Change from visit 2 (baseline) to visit 8 in global disease activity
- Change from visit 2 (baseline) to visit 8 in global improvements in knee problem, knee pain and knee function
- Change from visit 2 (baseline) to visit 8 in quality of life (QOL)
- Change from visit 2 (baseline) to visit 8 in MRI bone marrow lesion volume
- Change from visit 2 (baseline) to visit 8 in MRI cartilage thickness loss
- Change from visit 2 (baseline) to visit 8 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- Change from visit 2 (baseline) to visit 8 in patient-reported e-diary daily recall knee joint pain
- Change from visit 2 (baseline) to visit 8 in patient-reported e-diary daily recall analgesics use
- Changes from visit 2 (baseline) to visit 8 in serum biomarkers C-terminal telopeptide of collagen type I (sCTX-I for bone resorption assessment) and urinary C-terminal telopeptide of collagen type II (uCTX-II for cartilage degradation assessment)
-

Exploratory endpoints:

- Changes from visit 2 (baseline) to visit 8 in the serum and urinary biomarkers (Procollagen type I N-terminal propeptide [sPINP], bone specific alkaline phosphatase [sBSAP], N-terminal telopeptide of collagen type I [uNTX-I], uCTX-I, uαCTX-I and Tartrate-resistant acid phosphatase 5b [sTRAP5b])
- Pharmacokinetics: MIV-711 Pharmacokinetic (PK) parameters and their relationship to covariates such as age, weight, gender, liver function and concomitant medications.
- Change from visit 2 (baseline) to visit 8 in compound index of MRI bone area and cartilage thickness

Safety:

Safety endpoints:

- Incidence and severity of adverse events
- Incidence and severity of clinical laboratory abnormalities
- Summary of changes in physical examination compared to baseline by patient
- Mean change from visit 2 (baseline) in vital signs (blood pressure, heart rate and temperature)

- Categorical summary of absolute vital signs and vital sign changes compared to visit 2 (baseline) by patient

Statistical Methods

Primary Efficacy analysis

Change from baseline in NRS pain score will be analysed using a linear mixed model analysis based on the full analysis set (FAS) (modified intention to treat [mITT]). Only post-baseline NRS values will be used as the dependent variables. Baseline NRS will be included as a covariate. The model will include treatment group, baseline value, chronic analgesic use, minimization factors, week and week treatment group interaction as fixed effects and site as random effect. Development over time will be summarised by graphs (Least square means [LSmeans] and 95%-confidence limits as appropriate).

Secondary Efficacy analysis

All analyses of secondary endpoints will be conducted using same statistical model as specified in the primary efficacy analysis, adjusting for the same covariates as the primary analysis. The mITT population will be used for all secondary analyses.

Secondary efficacy endpoints recorded at visit 2 (baseline) and visit 8 will be analysed using an analysis of covariance (ANCOVA). The model will include treatment group, baseline value, chronic analgesic use, minimization factors and site. Least square means (LSmeans) and the estimate of the difference between the treatment groups will be provided along with a 95% confidence interval (CI) and p-value. In the analysis of biomarkers that are sampled at multiple visits, all sampled time points will be considered for change from baseline and comparison to placebo in the respective cases.

All secondary outcomes will be summarised descriptively (mean, standard deviation [SD], median, minimum and maximum for continuous data and counts and percentages for categorical data).

For the analysis of all primary and secondary efficacy endpoints, alternate statistical methods maybe considered that will include the use of generalised linear models that account for the response variable having a “non-normal” distribution.

Exploratory analysis

The exploratory analysis of additional bone and cartilage biomarkers, PK and imaging above are not part of the statistical analysis set and will therefore be listed and may therefore be reported separately.

The biological samples used for possible exploratory analysis (above) may be retained at Medivir, Huddinge, Sweden, or at an affiliated storage location detailed in the Laboratory Manual, for a maximum of 5 years following the finalisation of the Clinical Study Report. The results from such analysis will be reported separately from the Clinical Study Report.

Safety analysis

Safety summaries will be presented by treatment group and scheduled assessment for the Safety Analysis Set (SAF). Summary statistics (number of observations, mean, standard deviation, median and minimum and maximum values) will be presented by treatment group for continuous variables, and number and percentages (n, %) will be presented by treatment group for categorical variables. Treatment-emergent adverse events (TEAEs) will be summarised according to the coded Medical Dictionary for Regulatory Activities (MedDRA), preferred term and system organ class.

Clinical laboratory tests (hematology, serum chemistry, ECG and vital signs) will be summarised by treatment group for the SAF at each applicable scheduled assessment for the SAF. Potentially clinically important findings will be summarised by treatment group and listed.

No formal interim analysis to allow early stopping of the study on the basis of demonstrating efficacy or futility is planned. Unblinded Interim safety analyses (i.e. no efficacy analyses) will be undertaken after 50, 100, 150 and 200 patients have completed visit 6.

LIST OF STUDY PERSONNEL

Sponsor	Medivir AB Blasieholmsgatan 2 111 48 Stockholm, Sweden
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Laboratory for safety testing and urinalysis	ACM Global Central Laboratory 23 Hospital Fields Road York, YO10 4DZ, United Kingdom
Laboratory for biomarker analysis	Nordic Bioscience Laboratory A/S Herlev Hovedgade 207 2730 Herlev, Denmark
Laboratory for drug concentration analysis	York Bioanalytical Solutions Cedar House, Northminster Business Park Upper Poppleton York, YO26 6QR, United Kingdom
eDiary provider:	CRF Health Brook House - 3rd Floor 229-243 Shepherds Bush Road Hammersmith London, W6 7AN, United Kingdom

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- Total blood volumes

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviation and special terms are used in this Clinical Study Protocol.

ACLT	Anterior cruciate ligament transection
ACR	American College of Rheumatology
AE	Adverse event
ANCOVA	Analysis of covariance
Anti-HBc	Total Hepatitis B core antibody
Anti-HBs	Antibody to Hepatitis B Surface Antigen
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the concentration-time curve from zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from zero to infinity
BSAP	Bone specific alkaline phosphatase
BML	Bone Marrow Lesions
DMEC	Data Monitoring and Ethics Committee
CI	Confidence interval
C_{max}	Observed maximum measured plasma concentration
CRA	Clinical research associate
CRO	Contract research organisation
CTX-I	C-terminal telopeptide of collagen type I
CTX-II	C-terminal telopeptide of collagen type II
eCRF	Electronic case report form
EDC	electronic data capture
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-5L	EQ-5D is a standard measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal
FAS	Full analysis set
FTIM	First time in man
FSE	Fast spin echo
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

IB	Investigator's brochure
ICF	Informed consent form
ICOAP	Intermittent and constant osteoarthritis pain
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JSN	Joint space narrowing
K-L grade	Kellgren and Lawrence grade
LSmeans	Least square means
M1	MIV-711 metabolite MV078617
M2	MIV-711 metabolite MV077555
MedDRA	Medical Dictionary for Regulatory Activities
MF	Medial femoral
MOAKS	MRI Knee Osteoarthritis Score
MRI	Magnetic resonance imaging
mITT	modified intention to treat
NSAID	Nonsteroidal anti-inflammatory drug
NOAEL	No observed adverse effect level
NRS	Numeric rating scale
NTX-I	N-terminal telopeptide of collagen type I
OA	Osteoarthritis
OAQoL	Osteoarthritis Quality of Life questionnaire
OARSI	Osteoarthritis Research Society International
OD	Once-daily
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OP	Osteoporosis
OVX	Ovariectomy
PD	Proton density
PINP	Procollagen type I N-terminal propeptide
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported outcomes
QoL	Quality of Life
QTcF	QTc interval (Fridericia's correction)

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
sBSAP	serum Bone specific alkaline phosphatase
SD	Standard Deviation
sPINP	serum Procollagen type I N-terminal propeptide
sCTX-I	serum C-terminal telopeptide of collagen type I
sTRAP5b	serum Tartrate-resistant acid phosphatase 5b
SUSAR	Suspected unexpected serious adverse reaction
Target Knee	Identified by knee pain on a numeric rating scale and Kellgren and Lawrence classification grade. If patients have knee pain in both sides with equal regard to these two criteria, the right knee should always be prioritized.
TE	Time-to-echo
TEAE	Treatment-emergent adverse event
$t_{1/2}$	half-life time
uα CTX-I	Urine α C-terminal telopeptide of collagen type I
uCTX-I	urine C-terminal telopeptide of collagen type I
uCTX-II	Urine C-terminal telopeptide of collagen type II
ULN	Upper limit of normal
uNTX-I	urine N-terminal telopeptide of collagen type I
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1 INTRODUCTION

1.1 Abstract

Knee Osteoarthritis (OA) represents a major health burden with few effective analgesic therapies and no approved structure modification drugs. The subchondral bone is integral to the OA process with modern imaging studies showing that subchondral bone pathology is associated with both the symptoms and progressive loss of cartilage in knee OA. The available data support the hypothesis that a potent and selective inhibitor of cathepsin K such as MIV-711 will have both anti-resorptive effects on subchondral bone and protective effects on cartilage and animal models demonstrate reduced structural joint degradation. MIV-711 has now completed Phase I and the intention is to conduct a three-arm 240 patient, 6 month, Phase IIa, randomised, placebo-controlled study to determine the efficacy of MIV-711 in treating painful, radiographic knee OA, both in terms of symptoms and structural progression.

1.2 Background

Osteoarthritis is the fastest growing chronic pain disease worldwide.[2, 3] Radiographic knee OA is the most frequent site and affects about one in four middle age and older men and women.[4] Symptomatic knee OA (defined as frequent knee pain and an X-ray showing OA) affects about 12% of persons aged 55 years and over. Current treatments for OA are aimed at controlling pain, and all major contemporary evidence-based guidelines recommend a range of pharmacological and non-pharmacological therapies.[5, 6, 7, 8] Other than surgery, there are no current safe, long-term, effective analgesic treatments for established OA; consequently 70% of people with OA report to being in constant pain and 12.5% live with daily unbearable pain. [5, 9, 10]

A growing literature has suggested benefits for agents targeting OA subchondral bone.[11, 12] Bisphosphonates are commonly used for treating conditions with exaggerated osteoclastic bone resorption including osteoporosis, but also indicate beneficial effects in OA.[13, 14, 15] Treatment with strontium ranelate, another anti-resorptive bone acting agent which enhances pre-osteoblast replication, promotes osteoblastic differentiation and inhibits osteoclastic activity, was associated with a significant effect on structure, with a smaller loss of joint space width over 3 years compared with placebo.[16, 17, 18] Current studies of structure modification for regulatory approval use radiographic joint space width as the primary outcome which requires large numbers of patients over long periods of time.

Magnetic resonance imaging (MRI) has provided new insights into the multi-tissue pathology underlying typical clinical OA, and has also provided novel imaging biomarkers.[19, 20, 21] While cartilage quantification and morphology have been well studied, semi-quantitative measures of other tissues are slowly accruing evidence for their metric properties in clinical studies.[22] Recently, a publication showed that accurate 3D quantification of MRI bone area provides a valid and highly responsive measure of OA progression and in a small study which selected for typical clinical study patients, bone area was more responsive to change at 3 and 6 months than quantitative cartilage measures.[23, 24, 25]

Cathepsin K is a cysteine protease predominantly expressed in the osteoclast and intimately involved in bone resorption. It is also expressed in chondrocytes and synovial fibroblasts. Under normal physiological conditions, cathepsin K degrades key bone matrix proteins such as type I collagen. Cathepsin K is also expressed in chondrocytes in cartilage where it is able to cleave collagen type II and aggrecan, the main components of the cartilage matrix, leading to cartilage destruction. Consistent with these observations, transgenic mice that over-express cathepsin K spontaneously develop synovitis and cartilage degeneration.[26] Some fragments

resulting from Cathepsin K cleavage serve as biomarkers for its activity both *in vitro* and *in vivo* as further described below.
Cleavage of type I collagen results in release of the C-terminal telopeptide of collagen type I (CTX-I), a biomarker that has been used extensively as a surrogate measure of bone resorption.[27] Cartilage degradation can be assessed by measuring the C-terminal telopeptide of collagen type II (CTX-II), which is a fragment released during cartilage degeneration in OA. In OA patients, increased CTX-II levels are associated with loss of cartilage integrity and are linked to disease burden, progression and radiographic scoring.[12, 28, 29] Bone-acting agents do not solely affect CTX-I but also CTX-II, most likely indirectly due to their anti-resorptive effects on subchondral bone. Reductions in CTX-II levels of 20-40% by anti-resorptive drugs are associated with attained pain and structural primary endpoints in OA patient studies.[14, 16, 30, 31] To summarise the relevance of these two biomarkers, the reduction of CTX-I and CTX-II in blood and urine are used as indicators of reduced bone resorption and collagen degradation, respectively, which are believed to translate into beneficial effects counteracting joint degeneration in OA.
Besides effects on biomarkers under physiological conditions, pharmacological studies performed in surgically-induced OA models *in vivo* have demonstrated that cathepsin K inhibition reduces cartilage degeneration, prevents subchondral bone loss and attenuates osteophytosis in rabbits subjected to anterior cruciate ligament transection (ACLT). [32] In addition, cathepsin K inhibition reduces cartilage degeneration in dogs subjected to partial medial meniscectomy, another experimental model of OA.[33] Cathepsin K inhibition also reduces the mechanosensitivity of knee afferent nerve activity in a guinea pig model of spontaneous OA, thus suggesting a role for cathepsin K in joint nociception during disease progression.[34]
The investigational product intended for the present study, MIV-711, is a potent, selective and reversible inhibitor of the cathepsin K enzyme with an attractive preclinical profile. A consistent relationship is observed between the magnitude of MIV-711-evoked reductions on CTX-I and CTX-II and effects on disease progression in different animal models of OA.[32, 33] The MIV-711 biomarker results in man (described briefly in section 1.3 and in dosing rationale section), show changes in CTX-I and CTX-II levels of similar magnitudes to those that are associated with disease modification in the animal models of OA. Hence, a positive effect of MIV-711 treatment on structurally relevant readouts in OA may be expected. More detailed information of MIV-711's pharmacology, pre-clinical studies including OA animal models and Phase I clinical testing are further detailed in the Investigator's brochure (IB).

1.3 Pharmacokinetic, Pharmacodynamic and Safety results from MIV-711 first in man study

A First Time in Man (FTIM) study with MIV-711 has been conducted in male and female healthy volunteers including single doses up to 600 mg, multiple doses up to 200 mg once-daily (OD) for 7 days and in healthy post-menopausal female volunteers at multiple doses of 100 mg OD for 28 days. The single dose part enrolled 18 males and 9 females with the age range 19-64 years. The multiple dose parts enrolled 15 males and 24 females with the age range 18-65 years. The primary objective was to determine the safety and tolerability of ascending single and multiple oral doses of MIV-711 in healthy volunteers.
MIV-711 was rapidly absorbed after oral administration with peak concentrations typically occurring 1 hour after administration. A high fat meal prolonged the absorption but had no apparent effect on systemic exposure measured by area under the concentration-time curve from zero to infinity (AUC_∞) of MIV-711. The mean terminal half-life ($t_{½}$) was 3.3 to 5.2 hours over the 20 to 200 mg dose range. Observed maximum measured plasma concentration (C_{max}) and AUC_∞ increased in close proportion to dose over the single dose range 100-600 mg. Following multiple oral administration of 50 to 200 mg OD for 7 days or

100 mg OD for 28 days, no accumulation of MIV-711 was observed. MIV-711 was indicated to be extensively metabolised with less than 1% excreted unchanged by the kidney. No gender differences in dose normalised C_{max} or AUC_{∞} for MIV-711 were observed. Further details on MIV-711 metabolism can be found in the IB.
A dose-dependent reduction in the biomarkers serum CTX-I and urinary CTX-II was observed after single and multiple doses of MIV-711, by down to 55 and 72% from baseline respectively at multiple dosing (see further section 1.6 and the IB).
No clinically meaningful effects on vital signs, laboratory parameters or electrocardiogram (ECG) time intervals: including QTc interval (Fridericia's correction; QTcF) were observed. Adverse events (AEs) assessed as related to investigational medicinal product (IMP) had a similar incidence for active treatment and for placebo. One subject was found on a routine ECG to have asymptomatic atrial fibrillation after 3 OD doses of MIV-711 200 mg. Spontaneous conversion to sinus rhythm occurred within 24 hours after the last dose. Investigations by an independent cardiologist supported that the post-dose atrial fibrillation observed was possibly drug induced. Further details of the results of the FTIM study are provided in the IB.

1.4 Study rationale

As stated in section 1.2, there are no treatments available today that provide long term relief of OA symptoms nor are there any treatments that counteract its structural progression. Disease modifying OA drugs (DMOADs) would potentially address both these features which highlights the importance of evaluating candidate drugs such as MIV-711.

The available data support the hypothesis that a potent and selective inhibitor of cathepsin K such as MIV-711 will have both anti-resorptive effects on subchondral bone and protective effects on cartilage and animal models demonstrate reduced structural joint degradation. This first in patient study has the potential to establish a first indication of disease modifying efficacy for MIV-711 in OA and as such constitutes a first step to addressing a major unmet medical need.

1.5 Study design rationale

Since OA is a chronic, lifelong disorder of slow joint deterioration, disease modifying treatments would be expected to counteract the gradual structural worsening over longer periods of time which in turn makes a parallel design necessary. At the same time, the expected treatment lengths for efficacy in the clinical setting constitute one of two important limitations for early development OA patient in disease modifying osteoarthritis drug (DMOAD) trials. The second limitation is constituted by the long response time and poor sensitivity of presently used joint structure measures. Joint space narrowing (JSN) attenuation together with analgesic/symptom efficacy are currently requirements for putative structure modifying therapies in OA in that an analgesic effect could be expected to be concomitant to structural improvement (note the present study is not for pivotal purposes).[35]

It has been shown that previous studies employing either JSN-or magnetic resonance imaging (MRI-based cartilage thickness endpoints), require at least 300 patients/arm to have sufficient powered (Bowes et al. already in ref list) with treatment lengths of 12 months or more. This makes a limited size Proof of Concept (PoC) type study impossible with the associated difficulty in transitioning from Phase I to Phase II for a new entity drug in this indication.

Considering what is described above, pain has been chosen as the primary endpoint of this 6-month study since it could be expected to be an earlier read-out than the mentioned typical radiological endpoints, as well as being less demanding in terms of sample size. In order to get the possibility for a joint structural read-out, none of the typical radiological endpoints

would provide reliable data considering the sample size and treatment length of the present study. Instead, as key secondary endpoint this design employs an innovative and potentially more sensitive MRI joint bone surface measurement (see sections 6.1.2).[23] MRI bone surface measurements are untried in the interventional setting, but epidemiological data suggests a sensitivity of measure that in fact is sufficient for the present sample size.[23]

The suggested future application of MIV-711 in OA is that of a disease modifying drug which will be assessed in the present study as efficacy on knee joint pain and MRI joint structure as outlined above, which in turn governs the population selection rationale. The patients who enter this study therefore need to have a clinically significant chronic OA knee pain which is included on the basis of average pain symptoms ≥4 on the numeric rating scale (NRS) as well as a manifest radiographic OA expressed as K-L grade 2-3.[36] K-L grade 1 is excluded due to the very mild type of OA changes and long progression time that are indicative of this grade, whereas K-L grade 4 is judged to be too far along for the study of disease modification at least in the time frame of this study.

1.6 Dosing rationale

The single dose ranges of 20-600 mg and multiple dose ranges 50-200 mg MIV-711 given OD for 7 days have been explored in healthy volunteers. In addition, the 100 mg dose was administered OD in a 28-day open care cohort consisting of healthy post-menopausal female volunteers. In these settings, MIV-711 showed acceptable safety and tolerability in conjunction with no clinically significant changes in haematology, clinical chemistry, vital signs or ECG parameters. At 200 mg OD, AUC_{0-24} was on average 2.4 µM*h, i.e. 6 times lower than the no observed adverse effect level (NOAEL) in the 6 months monkey study.

Based on data from other bone acting agents (as described below), it is hypothesised that higher doses of bone-modifying agents may be required to achieve cartilage protection in OA compared to treatment of osteoporosis (OP).

- It has been shown that the bisphosphonate alendronate produces bone-protective effects in the ovariectomised (OVX) rat model (a model of estrogen-deficient OP) at relatively low doses, while higher doses are required to produce cartilage protective effects in the rat ACLT model (a model of OA). Briefly, 30 µg/kg/week alendronate (which is close to the clinical dose of 70 mg/week for OP) was sufficient to protect against bone loss in OVX-rats [37] while only providing mild cartilage-protective effects in ACLT rats. [38] By contrast, 240 µg/kg/week alendronate was required for optimal cartilage protection and prevention of osteophyte formation. [38]
- A similar pattern was found when using the cathepsin K inhibitor L-006235 in rabbit models of OP and OA. An oral dose of 10 mg/kg L-006235, given OD, provided complete bone protection in OVX-rabbits while a dose of 50 mg/kg was required to provide cartilage protection in ACLT-rabbits. [32,39]
- Similar findings have been demonstrated with strontium ranelate. A dose of 625 mg/kg/day was sufficient for bone protection in rats with or without OVX-evoked OP. [40] However, in an animal model of OA (medial meniscal tear, MMT), a dose of 1800 mg/kg/day was required to reduce subchondral bone remodelling and prevent articular cartilage degeneration.[41]

In summary, data from preclinical models indicate that higher doses of alendronate, strontium ranelate and the cathepsin K inhibitor L-006235 are required in order to achieve cartilage protection in OA compared to the treatment of OP.

While serum CTX-I levels are primarily a marker of bone resorption, urine CTX-II levels reflect cartilage degradation. In the clinical study MIV-711 reduced serum CTX-I levels were

observed in a dose-dependent manner by up to 79% after single doses of 20-600 mg, and by up to 55% after multiple (7 days) doses of 50-200 mg, compared to baseline. The effects were statistically significant at all dose levels, compared to placebo. The effect on CTX-I was closely related to the MIV-711 plasma concentrations. For CTX-II a dose-dependent decrease in urinary excretion after 7 days of dosing was observed. The mean decrease was 31%, 58% and 72% in subjects receiving 50, 100 and 200 mg MIV-711, respectively, compared to baseline, and the effects were statistically significant compared to placebo. After 28 days dosing at 100 mg OD the mean decrease was 67% for serum CTX-I and 55% for urine CTX-II compared to baseline.

MIV-711 has shown a higher reduction in CTX-II excretion at 200 mg compared with 100 mg OD. Based on the established link in literature and preclinical models, between CTX-II and the levels that are predictive for structural effects on bone only and the higher levels that are indicative of cartilage protection (see above and section 1.2), it is judged that the 200 mg dose should be studied in addition to the 100 mg dose since it has the highest potential to contribute to a disease modifying effect in OA. Both dose levels have been shown to be safe and tolerable in man as described above.

1.7 Risk-Benefit Assessment

The presently proposed Phase IIa, first-in-disease study will be the second clinical study with MIV-711 and as such it has the potential to determine the efficacy of MIV-711 in treating painful, radiographic knee OA, both in terms of symptoms and structural progression.

The toxicity of MIV-711 has been studied in mouse and monkey up to 6 months. In the mouse 6 month study, MIV-711 was well tolerated to systemic exposures of 58 µM*h (mean) in terms of AUC_{0-t} with no treatment-related microscopic findings. In the 6-month cynomolgus monkey study, the majority of the observed findings were related to MIV-711 pharmacology and the systemic exposure at NOAEL was 15 µM*h (mean) in terms of AUC_{0-24}. Further data is provided in the IB.

The single dose ranges 20-600 mg and multiple dose ranges 50-200 mg of MIV-711 given OD for 7 days have been explored in healthy volunteers. In addition, the 100 mg dose was administered OD in a 28-day open care cohort consisting of healthy post-menopausal female volunteers. In these settings, MIV-711 showed acceptable safety and tolerability in conjunction with no clinically significant changes in haematology, clinical chemistry, vital signs or ECG parameters.

The study of 200 mg MIV-711 OD in man (highest dose in present study) resulted in a 2.4 µM*h average AUC_{0-24} which concludes to an expected 6 times margin to the NOAEL level in the cynomolgus monkey.

In the multiple doses part of the Phase I study, MIV-711 was administered at dose of 100 mg OD for one month and 200 mg OD for one week. In the present study, both doses are given for a total duration of 6 months, which constitutes a significantly longer exposure compared to the Phase I study. The treatment length is driven primarily by the nature of OA and it is judged that 6 months is the minimum time needed to assess any effect of a bone acting agent in this disease. Considering the gap in existing safety data from one week up to 6 months, frequent visits and intermittent telephone contacts that include safety follow-up procedures have been scheduled as well as recurring Data Monitoring and Ethics Committee (DMEC) meetings reviewing the safety and tolerability data. The DMEC will reconvene at least at 4 occasions as 50, 100, 150 and 200 patients reach 14 weeks treatment (the DMEC may decide on more frequent meetings at its discretion).

MIV-711 has consistently shown efficacy in the Phase I study on the biomarkers that correlate strongly with efficacy on joint structure in the pre-clinical models. The doses of MIV-711 to be used in this study are estimated to provide an exposure sufficient to produce an

improvement in joint structure and symptoms, as has been shown for other bone-acting agents (see section 1.2 and section 1.6). There is a potential symptom and structure improvement benefit for patients participating in this study even though the treatment length is limited to 6 months. There is a potential for benefit together with the favorable safety and toxicology profile converge into a favorable Benefit/Risk assessment for present study.

With regard to previous clinical experience (see IB for further information), there are in present time no approved Cathepsin K inhibitors on the market, although several have been/are in clinical stages of development. The clinical data on these other compounds are only available in part from meeting abstracts and published progress reports. However it is judged that there is no indication of any class effect, or otherwise collectively significant findings in the available data that would infer any added risk to the Benefit/Risk assessment for the conduct of the present study.

On the basis of the pre-clinical and clinical data on MIV-711 up to this point and the result of Benefit/Risk balance, it is considered appropriate to proceed with the Phase IIa clinical study which is proposed in the present protocol.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the effect of MIV-711 on target knee average pain over 26 weeks as measured by an 11-point numerical rating scale (1 week recall) in patients with symptomatic and radiographic knee osteoarthritis.

2.2 Key Secondary Objective

To assess the effect of MIV-711 on MRI target knee bone area in patients with symptomatic and radiographic knee OA over 26 weeks.

2.3 Secondary Objectives

To assess, in patients with symptomatic and radiographic knee OA, over 26 weeks:

- The effect of MIV-711 on worst target knee pain (1 week recall)
- The effect of MIV-711 on average contralateral knee pain (1 week recall)
- The effect of MIV-711 on constant and intermittent OA pain
- The effect of MIV-711 on global improvements in knee problem, knee pain and knee function
- The effect of MIV-711 on knee joint OA symptoms (function, pain, stiffness)
- The effect of MIV-711 on global disease activity
- The effect of MIV-711 on quality of life (QOL)
- The effect of MIV-711 on MRI bone marrow lesion volume
- The effect of MIV-711 on MRI cartilage thickness loss
- The effect of MIV-711 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- The effect of MIV-711 on patient reported e-diary daily recall knee joint pain
- The effect of MIV-711 on patient reported e-diary daily recall analgesics use
- The safety and tolerability of MIV-711
- The effect of MIV-711 on biomarkers for bone resorption (serum CTX-I) and for cartilage degradation (urine CTX-II) assessment

2.4 Exploratory Objectives

In addition, the study will address the following exploratory parameters:

- Assessment of the effect of MIV-711 on exploratory serum and urinary biomarkers of relevance for OA including but not limited to Procollagen type I N-terminal propeptide (sPINP), bone specific alkaline phosphatase (sBSAP), N-terminal telopeptide of collagen type I (uNTX-I), uCTX-I, uαCTX-I and tartrate-resistant acid phosphatases(TRAP5b).
- Baseline (visit 2) and steady state treatment (visit 8) blood and urinary samples will be stored for patients who sign a separate voluntary Informed Consent Form (ICF) for potential future pharmacogenomics and disease-related proteomic, genomics, metabolomics and lipidomics analyses.
- The effect of MIV-711 on a compound index of MRI bone area and cartilage thickness
- The pharmacokinetics and metabolism of MIV-711 and the relationship to patient factors and concomitant medications.

3 OVERALL DESIGN AND PLAN OF THE STUDY

This is a multicentre, randomised, placebo-controlled, double-blind, three-arm parallel, Phase IIa study to evaluate the efficacy, safety and tolerability of MIV-711 in patients with symptomatic and radiographic knee OA.

The clinical study, which involves the use of an IMP, has been designed and will be run in accordance with the principles of Good Clinical Practice (GCP) and the current regulatory requirements as detailed in the Clinical Trial Directive 2001/20EC and any subsequent amendments of the clinical study regulations.

This Clinical Trial of an Investigational Medicinal Product - the data monitoring, clinical governance, quality assurance and ethical considerations will be performed in accordance with the Medicines for Human Use (Clinical Trials) Regulations (2004 and subsequent amendments) and principles of GCP.

A total of 240 patients with knee OA meeting the eligibility criteria and who provide written informed consent will be randomised on a 1:1:1 basis to the intervention (MIV-711 low dose 100 mg or high dose 200 mg) or placebo.

Interventions

The study will consist of two intervention arms and one control arm:

Intervention arm I: Patients will receive an once-daily 100 mg oral dose of MIV-711 for 26 weeks in addition to their current medication.

Intervention arm II: Patients will receive an once-daily 200 mg oral dose of MIV-711 for 26 weeks in addition to their current medication.

Control arm: Patients will receive an once-daily oral dose of matching placebo for 26 weeks in addition to their current medication.

MIV-711 (100 mg and 200 mg) and placebo will be provided as identical capsules.

All arms: Patients will be permitted to remain on their current analgesic regimen (patient's usual dose should remain the same for at least 4 weeks prior to study entry), with any changes in concomitant medications reported and recorded at study visits as well as in a patient reported daily e-diary for two week periods prior to visit 2 (baseline), visit 6 and visit 8.

The study consists of a screening period of approximately 4 weeks (visit 1), a baseline assessment period at visit 2, a double-blind treatment period of visit 2 through visit 8, and a follow-up period of 4 weeks (visit 9) after the last dose of study treatment is administered (see Figure 1).

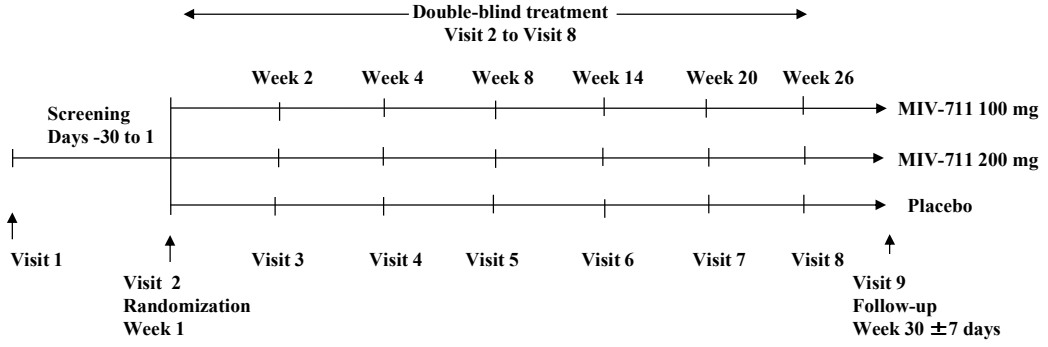

Figure 1: Schematic of study design

4 STUDY POPULATION

The study population will consist of patients with symptomatic and radiographic knee OA. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for enrolment in this study:

1. Current average knee pain, defined as pain in either knee, within 1 week before Visit 1, for which the patient gives a severity score of ≥4, <10 on a 0-10 NRS.
2. Inclusive of 40-80 years old.
3. Diagnosis of primary knee osteoarthritis, based upon the following:
   - Fulfilling the American College of Rheumatology Clinical and Radiographic (ACR) criteria for OA defined as knee pain for most days of the prior month and at least one of the following three factors: age >50 years, morning stiffness of less than 30 minutes and knee crepitus on motion.
   - X-ray evidence within the last 12 months for Kellgren and Lawrence (K-L) classification grade 2 or 3.
4. Female patients must be non-pregnant, non-lactating and of non-childbearing potential either as naturally (spontaneously) post-menopausal or due to hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy (as determined by patient medical history). Naturally (spontaneously) post-menopausal is defined as being amenorrhoic for 12 months without an alternative medical cause and with a screening follicle stimulating hormone indicating post-menopausal state.
5. Male patients should avoid fathering a child by either of the following methods:
   - True sexual abstinence: meaning that heterosexual abstinence is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence such as that based on calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of a trial, or withdrawal/coitus interruptus are not acceptable methods of contraception).
   - Willingness to use two effective means of contraception with their partner from the time of first IMP administration until 3 months after the last dose of IMP. Two or more of the following methods are acceptable and must include at least one barrier method: i) Surgical sterilisation (i.e., bilateral tubal ligation for female partners; vasectomy for male), ii) placement of an intrauterine device or intrauterine system, iii) hormonal contraception (implantable, patch, oral), iv) barrier methods including condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Male patients who have been sterilised are required to use one barrier method of contraception (condom).
6. The patient's usual analgesic regimen (in case of use) should remain the same for 4 weeks prior to the signature of the informed consent form.
7. Needs to be able to communicate well with the investigators and staff.
8. Able to comply with the requirements of the study procedures and provide written informed consent prior to any study related procedures.

4.2 Exclusion Criteria

Patients will be excluded from enrolment in this study if they meet any of the following criteria:

1. The presence of any inflammatory arthritis (e.g., gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy) or any underlying condition, other than OA, that may result in abnormal cartilage and bone metabolism.
2. Any generalised pain condition that may interfere with the evaluation of the target knee pain (e.g., fibromyalgia) as judged by the investigator.
3. A history of cancer within the previous 5 years (except for cutaneous basal-cell or squamous-cell cancer resolved by excision and cancer in situ which are allowed).
4. Ongoing or a history of atrial fibrillation.
5. Currently receiving medication that affects cartilage or bone metabolism (hormone replacement therapy taken for more than 6 months is allowed).
6. Current or recurrent disease that could affect the action, absorption or disposition of MIV-711, or could affect clinical assessments or clinical laboratory assessments.
7. Any clinically severe or significant uncontrolled concurrent illness, which, in the opinion of the Investigator, would impair ability to give informed consent or take part in or complete this clinical study.
8. Known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.
9. A positive human immunodeficiency virus (HIV) antibody screen, a positive Hepatitis B surface antigen (HBsAg) screen, and/ or a positive Hepatitis C virus (HCV) antibody screen. A positive total Hepatitis B core antibody (anti-HBc) test in conjunction with a negative antibody to Hepatitis B Surface Antigen (anti-HBs) test.
10. History of alcohol or other substance abuse within the last year.
11. Use of an investigational product within 30 days prior to receiving the first dose of investigational product or active enrolment in another drug or vaccine clinical study.
12. Significant target knee injury or surgery within the 6 months preceding enrolment in the study.
13. A history of partial or complete joint replacement surgery in the target knee at any time, listed for knee surgery, or anticipating knee surgery during the study period.
14. Any factor which, in the opinion of the investigator, would jeopardise the evaluation or safety of the patient or be associated with poor adherence to the clinical study protocol (e.g., inability to complete study diary, poor tolerability of venipuncture or lack of adequate venous access for required blood sampling during the study period).
15. Use of intra-articular hyaluronic acid in the target knee within the 3 months preceding enrolment in the study.
16. Use of intra-articular, intra-muscular or oral corticosteroids in the 2 months preceding enrolment.
17. Commencement of non-pharmacological OA interventions within two months preceding enrolment.
18. Vulnerable patients, e.g., patients kept in detention, soldiers, and employees of the sponsor or the contract Research Organisation (CRO) with direct involvement in the proposed

study or other studies under the direction of the investigator or the CRO, as well as family members of the employees or the investigator.

19. Patients with contra-indication to MRI of the knee.

4.3 Patient Withdrawal and Replacement

In accordance with the Declaration of Helsinki, GCP, and International Conference on Harmonization (ICH) Guidelines and applicable regulations governing human subject protections, individual patients have the right to withdraw consent at any time without prejudice. At the time of withdrawal of consent, a full efficacy and safety evaluation will be performed if the patient consents.

Patients who withdraw will be asked about the reason(s) for withdrawal, and the presence of any adverse events (AEs) and will be asked to return for a follow-up visit (visit 9). An MRI scan should be competed if withdrawal is after visit 6.

If a patient is being withdrawn due to a suspected infection, no biological samples from this patient are allowed to be sent to the laboratory. Samples will be managed according to standard routines at the study site.

In case of discontinuation, the CRA should be informed as soon as possible.

If the patient has not yet received any IMP and discontinues from the study, the patient should not participate in any further study related procedure.

Patients who withdraw will return to routine care.

Patients must also be removed from the study by the Sponsor or Investigator for any reasons, including:

- The occurrence of pregnancy in a patient.
- Use of a non-permitted concomitant drug, as defined in Section 5.7.4 where the predefined consequence is withdrawal from the IMP.
- Taking another investigational medicinal agent during patients involvement in the study i.e., from qualification to EOT.
- Any violation of, or deviation from study protocol procedures which, in the judgment of the responsible physician, could adversely affect the patients or the integrity of the study including missing more than 7 consecutive doses or other evidence of significant non-compliance (excluding drug holidays or interruptions that were medically warranted).
- Any clinical AE, laboratory abnormality, inter-current illness or significant worsening of inter-current illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Patients who undergo target knee joint replacement during the treatment period will be withdrawn from the study and classified as treatment failures.
- Serum transaminases (ALT and/or AST) > 3 x upper limit of normal (ULN) AND total bilirubin > 2 x ULN (confirmed by subsequent repeat).
- ALT or AST > 3 x ULN (confirmed by repeat visit) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.
- QTcF > 500 msec or increase > 60 ms from time matched baseline (confirmed by repeat ECG).
- Occurrence of an exclusion criterion which is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the Principal Investigator and/or Sponsor.

In order to perform the modified intention to treat (mITT) analysis, and to enable safety analyses, all patients who discontinue their randomised medication will be asked to still complete their follow-up visit (visit 9) as outlined in the study schedule.

Patients who withdraw from the study will not be replaced.

In all cases, the reason(s) for withdrawal must be recorded on the electronic CRF (eCRF).

4.4 Planned Sample Size and Number of Study Centers

It is planned to recruit 240 patients at 6 centers in 6 countries for this study.

Recruitment will be completive across all 6 sites.

4.5 Patient Identification and Randomization

4.5.1 Patient Identification

The Principal Investigator will obtain signed, informed consent from the potential study patient before any study-specific procedures are performed.

After written informed consent has been obtained, each patient will receive a unique screening number. Enrolled patients who drop out of the study before randomisation will retain their screening number.

4.5.2 Randomisation Scheme

A total of 240 patients with knee OA meeting the eligibility criteria and who provide written informed consent will be randomised on a 1:1:1 basis to the intervention (MIV-711 low dose 100 mg or high dose 200 mg) or placebo.

The randomization allocation will be assigned through a centralized automated code holder that distributes the next available randomisation number on the randomisation list to the requesting site as described below.

Allocation of patients to the treatment groups will proceed through the use of an Interactive Response Technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR) system].

The study site will obtain the randomization number and container number assignment from the IRT system. The randomization number and the date on which the randomization number was assigned will be recorded on the eCRF. Once patient screening numbers, container numbers, and randomization numbers have been assigned, they cannot be reassigned.

4.5.3 Allocation/Randomisation of Patients to Treatment

Randomisation of patient to treatment will occur at visit 2 (baseline) after all screening procedures have been performed and eligibility for the study confirmed. Each randomised patient will receive a unique randomisation number. Randomization number allocated to any patient will not be reallocated to other patients if he/she terminates the study participation for any reason, regardless of whether IMP was taken or not.

Once patient screening numbers, container numbers, and randomisation numbers have been assigned, patients cannot be reassigned.

4.5.4 Procedures for Handling of Incorrectly Included Subjects

Patients who fail to meet the inclusion/exclusion criteria for this study should not, under any circumstances, be enrolled into the study. There can be no exceptions to this rule.

Where patients who do not meet the study criteria are enrolled in error, or incorrectly randomised, or where patients subsequently fail to meet the criteria for the study post

enrolment, the procedures in the protocol for the discontinuation of such patients must be followed (see section 4.3).

Once the error is identified a discussion must occur between the sponsor, the Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from the study. It needs to be ensured that all such decisions are appropriately documented.

4.6 Extension Protocol

All patients in the current study at the participating sites included in Extension Study MIV-711-202 will be given the opportunity to participate in the extension protocol provided that they meet the MIV-711-202 eligibility criteria.

5 STUDY DRUG

5.1 Investigational Drug

MIV-711 is provided as the hydrochloride (HCl) salt of MIV-711. The pre-clinical development laboratory code was MV076159. MIV-711 is manufactured by Niels Clauson-Kaas A/S, Farum, Denmark.

MIV-711 is formulated in hard gelatin capsules (size 0) at the strengths of 100 and 200 mg, expressed as MIV-711 free base. The included excipients are microcrystalline cellulose; Starcap 1500; Magnesium stearate and anhydrous colloidal silica. The capsule formulation is manufactured by Galenica AB, Malmö, Sweden.

For the placebo formulation, the excipient composition of the MIV-711 hard gelatin capsule is used, but the active substance is substituted with microcrystalline cellulose and Starcap 1500. The placebo formulation is manufactured by Galenica AB, Malmö, Sweden.

MIV-711 (100 mg and 200 mg) and placebo are provided as identical capsules.

5.2 Administration

Patients will receive OD 100 mg or 200 mg oral dose of MIV-711, or placebo for 26 weeks in addition to their current medication.

The IMP should be taken OD in the morning approximately 24 hours apart and swallowed whole together with a glass of water (approximately 200 ml) before breakfast; breakfast can be taken approximately one hour later. The first dose is administered at the site during visit 2 (baseline).

IMP should be dispensed during the visits and returned by the patients for drug accountability at visit 5, visit 6, and visit 8.

On days when the patient will visit the site the IMP must be taken at the site fasting (and not at home) and the time of the intake must be recorded in the source documents.

5.3 Packaging, Labeling and Storage

The capsules will be packaged in the white Duma high-density polyethylene (HDPE) containers with polypropylene (PP) caps.

The proposed shelf life for the IMP in this packaging is 24 months at room temperature 15 to 25°C.

The packaging and labeling of the blinded patient packages will be performed in accordance with GMP and national requirements. The labeling will fulfil GMP Annex 13 requirements and be translated into local language.

The label will include the following information:

- Name and address of the sponsor (Medivir).
- Dosage form, route of administration and quantity of dosage units
- Study code
- Kit ID
- Directions for use
- The name of the investigator
- Storage conditions
- Batch number
- Expiry date

- The following standard statements:

  "for clinical study use only"

  "keep out of reach of children"

Additional local requirement will be adhered to the country-specific labels in accordance with local regulations for each participating countries.

A temperature record must be maintained and the max/min temperature must be recorded during working days.

The investigator must immediately inform the clinical research associate (CRA) in case of any temperature excursions.

Shorter (≤ 24 hours) periods of storage outside this range is accepted if maximum temperature does not exceed 40°C.

5.4 Drug Accountability

The Investigator is responsible for maintaining accurate IMP accountability records throughout the study. The clinical research CRA will review the accountability records.

Each dispensing of IMP will be documented in the eCRF system.

The drug accountability log will include information such as amount dispensed and amount returned to the site. IMP returned to the site will be stored as outlined in protocol section 5.3. The returned products should be marked as "returned" and kept separate from the IMP not yet dispensed.

The destruction of IMP will be performed according to local requirements following sponsor approval.

5.5 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. All supplied IMP will be identical packaging and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or as a result of a regulatory requirement.

If possible, the Investigator should attempt to notify the Sponsor/Medical Monitor prior to contacting Interactive Web Response System (IWRS). All calls resulting in an unblinding event will be recorded and reported by the IWRS to the Medical Monitor and the Sponsor.

If the blind is broken, the date, time, and reason must be recorded in the patient's eCRF system, and any associated AE reported.

The overall randomisation code will be broken only for reporting purposes. This will occur once all interim/final clinical data have been entered onto the database and all data queries have been resolved, and the assignment of patients to the analysis sets has been completed.

5.6 Compliance

The administration of all medication (including IMP) must be recorded in the appropriate sections of the eCRF. The investigator is responsible for discussing the treatment compliance with the patient before randomisation. Drug accountability will be performed and compliance of drug accountability will also be discussed with the patient.

Treatment compliance will be analysed via capsule count. More details will be given in the Statistical Analysis Plan (SAP).

5.7 Other Medications

5.7.1 Rescue Medication

Where possible, patients will be asked to continue with the same analgesic or anti-inflammatory medication that they are taking at screening throughout the study. However, if a patient is experiencing increased or decreased pain and requires an increase or a decrease in the dose of analgesics, or an occasional change of analgesics medication, then this will be allowed, but the reason for the dose change, the new dose and or medication used, must be documented in the eCRF.

5.7.2 Concomitant Medications

In vitro studies have shown no significant inhibition of drug metabolic CYP enzymes at MIV-711 concentrations up to 10 μM. In a previous clinical study, mean C_{max} at steady-state for the dose 200 mg OD was 0.58 μM and the highest individual value was 0.80 μM. It is therefore considered unlikely that MIV-711 will affect the metabolism of other drugs through CYP inhibition and there are no specific restrictions on concomitant medications for pharmacokinetic (PK) reasons. Furthermore, clinical data indicate that MIV-711 is extensively metabolised potentially by several routes, making it less likely that other drugs should significantly affect the metabolism of MIV-711.

In addition to the periodical e-diary, use of concomitant medication and any non-pharmacological interventions will be recorded in the source document. All concomitant medications taken during the study will be recorded with generic name, indication, daily dose, and start and stop dates of administration at each visit. For this study, prescription medicines, other than those prohibited by the study protocol are permitted as concomitant medications to manage ongoing or chronic, stable medical conditions. Medications taken within 4 weeks of the screening visit will be documented as prior medication. Medication taken after the first dose of IMP will be documented as concomitant medication. Patients will be permitted to reinstate prohibited concomitant medications on completion of their final study visit. All patients will be asked about concomitant medication use and any changes to use of concomitant medications at all study visits.

5.7.3 NSAIDs and other analgesics

Patients will be allowed to continue any analgesic medication they are taking at the screening visit for the duration of the study. The patients' usual analgesics regimen should remain the same for 4 weeks prior to starting the study. Typical OA analgesics are allowed such as: nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and tramadol, as well as NSAID and paracetamol combinations with mild opioids such as codeine and dextropropoxyphene. In addition to the periodical e-diary, use of concomitant medication will be recorded in the source document at each visit.

5.7.4 Prohibited concomitant medications

Patients should not use any form of steroids (oral, intravenous, intra-articular or intra-muscular) during the study period; except for inhaled/intranasal steroids for the treatment of allergic rhinitis and/or asthma and topical steroids for the treatment of eczema. Medications purposed to affect bone or cartilage metabolism are also prohibited as exemplified (albeit not exhaustively) by antiresorptive medications such as bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL) inhibiting antibodies and

calcitonin. Apart from combinations with mild opioids as specified in section 5.7.3, all opioids are prohibited unless for occasional rescue medication purposes. In case of uncertainty regarding prohibited medications please contact the medical monitor.

5.7.5 Chondroitin and glucosamine

Patients will be permitted to continue current use of chondroitin and glucosamine; however their use must be clearly documented in the CRF. Chondroitin or glucosamine therapy may not be started during the study.

5.8 RESTRICTIONS

Due to the lack of data on the phototoxicity potential of MIV-711 when the study was started, patients participating in this study should be advised to take sun and UV-light protective measures for the duration of the study. Such measures include for example, avoiding indoor tanning and direct sun exposure especially between 10 am and 4 pm. If sun/UV light cannot be avoided, suitable protective clothing and use of appropriate sunscreen on uncovered areas of the skin are advised.

After this study started, further evaluation of MIV-711 in laboratory tests have meanwhile been undertaken and concluded that there is no phototoxicity risk for patients taking MIV-711. However, since this study is ongoing, patients will still be advised to follow the above described sunlight protective measures because it is important to keep as many conditions as possible similar during the course of the study.

6 ENDPOINT AND METHODS OF ASSESSMENT

6.1 Efficacy Endpoint

6.1.1 Primary Efficacy Endpoint

The primary outcome will be the change in the assessment of average pain score over the past 1 week for the target knee, between visit 2 (baseline) and visit 8, on a 0 - 10 NRS. The scale ranges from 0 indicating "no pain", to 10 indicating "pain as bad as it could be". Pain has been chosen as the primary outcome because according to regulatory guidelines, an admissible disease modifying effect in OA needs either to result in symptom efficacy (together with structural benefit) or decreased events in terms of surgical treatment. The latter cannot be determined in the present study due to insufficient length of follow up.

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) suggests that outcome measures for OA studies should include pain, function and QOL. The use of an 11 - point pain NRS as the primary outcome for OA pain studies is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [42, 43, 44, 45], as they have been found to be reliable and to demonstrate good face and criterion validity. [46]

6.1.2 Key Secondary Endpoint

The key secondary endpoint will be the MRI of bone area. Bone parameters will be measured for MRIs of the target knee taken at visit 2 (baseline) and visit 8.

6.1.3 Secondary Imaging Endpoints

MRIs will be analysed semi-quantitatively by a central experienced musculoskeletal radiologist using the MOAKS [47] and quantitatively using statistical shape modelling (SSM, Imorphics Ltd) for the features below. [23, 48, 49]

MOAKS scoring will be used to assess the following features:

- Bone Marrow Lesions (BMLs) and cysts - 15 subregions graded for BML (including ill-defined lesion and cysts) size in regard to the total volume of the subregion occupied by BML(s). Grade 0= none, grade 1<33% of subregional volume, grade 2=33–66% of subregional volume and grade 3>66% of subregional volume.
- Articular Cartilage - 14 articular cartilage regions graded for size of any cartilage loss (including partial and full thickness loss) as a % of surface area as related to the size of each individual region surface and % of loss in this subregion that is full-thickness loss.
- Osteophytes - 12 sites scored for presence and size of osteophytes. Grade 0=none; Grade 1=small; Grade 2= medium; Grade 3= large.

Statistical shape modelling will be used to assess:

- Mean cartilage thickness (mm) for each of the anterior, posterior and central regions, with areas denuded of cartilage included as having zero thickness [50]
- Bone marrow lesion volume (mm^3) by anatomical region: medial and lateral femorotibial region of femur, medial and lateral patellofemoral region of femur, medial and lateral tibia, and patellaBone area (mm^2) for anatomical regions: lateral and medial femur (patellofemoral); lateral and medial femur (femorotibial); lateral and medial patella, lateral and medial tibial condyle
- Bone shape by distance along an OA shape vector for femur, tibia and patella
- Index Bone area/Cartilage thickness.

6.1.4 Secondary Endpoints

Patient-Reported Outcomes (PRO)

PRO will be recorded using questionnaires as specified in Table 2.

- Average overall knee pain severity in the target knee over the past 1 week (0 - 10 NRS)
- Worst knee pain severity in the target knee over the past 1 week (0 - 10 NRS)
- Global disease activity over the past 1 week (0 - 10 NRS)
- Average overall knee pain severity in the contralateral knee over the past 1 week (0-10 NRS)
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 3.1 [51] - a 24-item OA-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in OA of the knee. The five responses are scored as 0=none, 1=mild, 2=moderate, 3=severe, 4=extreme. The 24 questions are divided into 3 subscales; pain (questions 1 - 5, score range 0 - 20), stiffness (questions 6 and 7, score range 0-8) and physical function (questions 8-24, score range 0 - 68). Higher scores indicate worse pain, stiffness and physical function. The subscale scores are derived by summing the assigned values on component items. The study joint referred in the WOMAC questionnaire corresponds to the target knee (as referenced elsewhere in this protocol).
- Osteoarthritis Research Society International (OARSI)-OMERACT Responder index [52, 53] will be calculated using the WOMAC pain and function subscales and the patient's global assessment score. Response will be defined as:

  1) Improvement in pain or function ≥50% and absolute change ≥20 or
  2) Improvement in at least two of the following:
     i) pain ≥20% and absolute change ≥10,
     ii) function ≥20% and absolute change ≥10 and
     iii) patients' global assessment ≥20% and absolute change ≥10
- Intermittent and constant osteoarthritis pain (ICOAP) [52] - an 11-item tool designed to assess constant and intermittent OA pain. The tool will be self-reported. (The tool was designed for telephone or interview administration but self-reporting is allowed.) The questions will be scored according to the User Manual [54] into a constant pain subscale, intermittent pain subscale and total pain score. These scores will be transformed to a 0-100 scale for analysis.
- Global improvements in knee problem, knee pain and knee function recorded on a 6-point likert scale: completely better, much better, better, no change, worse, much worse.
- EuroQol-5 Dimensions (EQ-5D-5L) [55] - a generic measure of self-reported health status that defines health status in terms of five dimensions – mobility; self-care; usual activity; pain or discomfort; and anxiety or depression [56]. EQ-5D-5L has been extensively validated and shown to be sensitive, internally consistent, and reliable in the general population and other patient groups, including for inflammatory arthritis.[57]
- In an e-diary format, a patient knee pain diary (NRS) and analgesia questionnaire will be completed daily during three two-week periods prior to visit 2 (baseline), visit 6 and visit 8. Baseline will be defined as the last observation prior to the first dose of investigational product. The assessments in the e-diary comprise.
  1) Average overall knee pain severity in the target knee over the past 12 h (0 - 10 NRS)
  2) Worst knee pain severity in the target knee over the past 12 h (0 - 10 NRS)

3) Adherence to usual analgesics regimen
4) Intake of IMP (note: in case the e-diary device is kept by the patients for the full duration of the study, intake of IMP will be registered daily throughout the study)

Laboratory assessments:

Blood and urine samples will be taken at visit 2 (baseline) and visit 4, visit 6, visit 8, and visit 9 for analysis of serum CTX-I and urinary CTX-II biomarkers.

6.1.5 Exploratory Endpoints

6.1.5.1 Biomarkers and biobanking

Blood and urine samples will be taken at visit 2 (baseline), visit 4, visit 6, visit 8, and visit 9 for analysis of exploratory bone and cartilage markers of relevance for OA disease such as sPINP, sBSAP and s(TRAP5b) in blood and uNTX-I, uCTX-I and uαCTX-I in urine. Pharmacogenomic samples will also be collected and stored to enable further profiling (proteomic, genomic).

A blood and urine sample from visit 2 and visit 8 will be collected and stored in a biobank according to local biobanking regulations and under a separate voluntary ICF, to enable further profiling (pharmacogenomics, proteomics, genomics, metabolomics and lipidomics). In addition, potential susceptibility genes and genes related to underlying disease may be explored using the same samples. Aliquots of each sample will be retained for up to 5 years by the sponsor or its subcontractor for biobank storage, in line with GCP/Good laboratory practice and biobanking policies.

Biological samples used for possible exploratory analysis may be retained at Medivir, Huddinge, Sweden, or at an affiliated storage location detailed in the Laboratory Manual, for a maximum of 5 years following the finalisation of the Clinical Study Report. The results from such analysis will be reported separately from the Clinical Study Report.

6.1.5.2 Imaging

Change from visit 2 (baseline) to visit 8 in a calculated compound index of MRI bone area (key secondary endpoint) and cartilage thickness.

6.1.5.3 Pharmacokinetics

The pharmacokinetics and metabolism of MIV-711 and the relationship to patient factors and concomitant medications will be analyzed following the sampling procedures as described in section 6.8.

6.2 Safety Endpoints

- Incidence and severity of adverse events
- Incidence and severity of clinical laboratory abnormalities
- Summary of changes in physical examination compared to baseline by patient
- Mean change from baseline in vital signs (blood pressure, heart rate, and temperature)
- Categorical summary of absolute vital signs and vital sign changes compared to baseline by patient

6.3 Physical Examination

A standard complete physical examination will be performed at visit 1 (screening), visit 2 (baseline), visit 5, visit 6 and visit 8. The following parameters and body systems will be examined and any abnormalities will be described: general appearance, skin (presence of rash), head, eye, ears, nose, and throat (HEENT), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremities exam for the presence of peripheral edema, abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

A targeted physical examination will be performed at visit 3, visit 4, and visit 7 assessing the following: lungs, heart, abdomen, extremity exam for the presence of peripheral oedema and lymph nodes. A standard clinical examination of both knees will be undertaken at all visits. Any clinically significant changes from visit 2 (baseline) should be recorded as AEs.

6.4 Vital Signs

Vital signs (body temperature, heart rate, blood pressure, oxygen saturation) will be performed at all clinic visits prior to IMP dosing.

Blood pressure and heart rate measurements will be performed after the patient has been resting in a supine position for at least 5 minutes.

Height will be measured at visit 1 (screening) and weight will be measured at visit 1 (screening) and visit 8.

6.5 12-lead Electrocardiograms (ECG)

A 12-lead ECG will be performed at all clinic visits.

12-lead serial ECGs will be recorded at visit 2 (baseline) pre-dosing and after 30 minutes, 1 hour and 2 hours post-dosing (± 10 minutes).

Standard 12-lead ECG will be performed at all other visits 30 minutes after dosing (± 10 minutes).

The 12-lead ECG will be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs will be assessed by the investigator, and the data will be recorded in the eCRF. The clinical significance of ECG results will be determined by the investigator after review of the ECG report in relation to the patient's medical history, physical examination findings, and concomitant medications.

6.6 Imaging Assessments

6.6.1 K-L Scoring

K-L scoring based on target knee radiographs no older than 12 months is required to assess inclusion criterion 3. This could be performed by a local radiologist and in order to ensure comparability and accuracy of study data and to evaluate variability between study sites, an independent consultant radiologist will review the K-L scoring on all patients from digitized images. In some instances there may be adjudication between the local and the independent radiologist's assessments, which is further detailed in the Imaging Investigator Site Operations Manual.

6.6.2 MRI Assessments

At visit 2 (baseline) and visit 8, MRI acquisition will be performed on the target knee using 1.5/3T systems using the following sequences, which have been optimised for visualization of

bone, cartilage and BML: high resolution 3D sagittal proton density (PD) fast spin echo (FSE) with fat saturation; sagittal PD FSE intermediate-weighted with fat-saturation; sagittal PD FSE without fat-suppression. The total scanning time for this set of sequences is approximately 15 minutes.

When obtaining the MRI scan the sites must use the same scanner and coil at both visit 2 and visit 8.

It will be the responsibility of each site to ensure robustness of MRI acquisition. At each centre, phantoms will be scanned and visually assessed for distortion, warping and double shadowing along with protocol compliance prior to study initiation and then regularly re-tested. It is the responsibility of the sites to perform these phantom scans on a regular basis throughout the study and these scans will not be evaluated centrally. In case of phantom scan image quality issues the phantom scans will be sent to PAREXEL Imaging for evaluation. If a site has an imaging-related upgrade (hardware/software) then a phantom scan will be requested before and after upgrade to confirm the protocol has not changed.

Each set of patient images will be quality controlled to allow for a repeat MRI to be captured if required.

Further details are provided in the imaging acquisition guidelines provided to each site.

Upon study completion the MRI measures from the images gathered for this study will be repeated using automated image analysis to enable future methodological improvements.

6.7 Self-report Parameters

Patient-reported outcomes will be recorded using questionnaires at visit 2 (baseline) and at visit 5, visit 6, and visit 8, as follows:

Pain, function and disease activity

At visit 2 (baseline), visit 5, visit 6, and visit 8:

- 11-point NRS scales for:
  - Average overall knee pain severity in the target knee over the past 1 week (also recorded at visit 9)
  - Average overall knee pain severity in the contralateral knee over the past 1 week (also recorded at visit 9)
  - Worst knee pain severity in the target knee over the past 1 week
  - Global disease activity over the past 1 week
- ICOAP – an 11-item tool designed to assess constant and intermittent pain
- WOMAC 3.1 – a 24-item OA - specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in OA of the knee
- In an e-diary format, a patient pain diary and analgesia questionnaire will be completed daily during three two-week periods prior to visit 2 (baseline), visit 6 and visit 8.

At visit 2 (baseline) only:

- Duration of knee pain over the past 12 months (within the last 7 days, 8-30 days, 31-92 days, >92 days)
- Onset of knee pain (within the last 12 months, >1 - 5 years, >5 - 10 years, >10 years)

At visit 5, visit 6, and visit 8 only:

Using a 6 - point Likert scale (completely better, much better, better, no change, worse, much worse) we will record patient-reported:

- Global improvement in knee problem at follow-up
- Global improvement in knee pain at follow-up
- Global improvement in knee function at follow-up

Quality of life

At visit 2 (baseline) and visit 8:

- EuroQol -5 Dimensions (EQ-5D-5L) - a generic measure of self-reported health status that defines health status in terms of five dimensions – mobility; self-care; usual activity; pain or discomfort; and anxiety or depression.

Clinical Safety Evaluation/Adverse Events

During each visit patients will be monitored and questioned by a member of the clinical staff for the occurrence of new adverse events since the last visit, or the outcome of any adverse events reported at previous visits. Incidence, severity, expectedness, relation to the study intervention and outcome of each adverse event will be documented and reported.

Adherence to Study Medication and Concomitant Medication

Patients will be asked to return any unused study medication at visit 5, visit 6, and visit 8 and drug accountability will be conducted. The Brief Medication Questionnaire self-reported measure [58] for the use of concomitant medication will be included at visit 5, visit 6, and visit 8.

6.8 Pharmacokinetics Sampling

Three blood samples will be collected at visit 4 and visit 8 to measure plasma concentrations of MIV-711. On each of these visits, one of these three samples will be collected at pre-dose and the other two samples will be collected post-dose. The two post-dose samples should be separated by two of the following time intervals, if possible; 0.25-1h, 1-2h, 2-4h, 4-6h, 6-8h and 8-10h. For example, if the first post-dose sample is taken at 1-2h the second should be taken at 6-8h.

The 3 blood samples (approximately 5 mL each) will be taken by venipuncture or cannulation from a forearm vein(s) and collected into a lithium heparin tubes, and will be mixed. After mixing, blood samples will be placed in a cool box containing crushed ice/water. The samples will be centrifuged, within 1 hour of collection, at 1500g for 10 minutes at approximately 4°C.

For each sample, the separated plasma will be equally split into 4 aliquots and transferred into 4 suitably labelled polypropylene tubes, and stored within 2 hours of collection at at least -70°C until shipped on dry-ice. Three aliquots will be dispatched to the Bioanalytical Laboratory for analysis of MIV-711 and for potential exploratory metabolite analysis. The forth aliquot will remain at the clinical site. Refer to the Laboratory Manual for further details.

The date/time of sample collection as well as the date/time of the most recent dose will be collected in the eCRF. A separate sub-protocol for the Population pharmacokinetics (PK) analysis will be established aiming at analyzing MIV-711 PK parameters and their relationship to covariates such as age, weight, gender, liver function, and concomitant medications. Exploratory PK-Pharmacodynamic analyses for efficacy variables and biomarkers may be performed based on the study results.

Further details on the provider and handling of the pharmacokinetic samples will be provided in the Laboratory Manual.

6.9 Biomarker Sampling

Blood and urine samples will be taken at visit 2 (baseline), visit 4, visit 6, visit 8 and visit 9 for analysis of serum CTX-I and urinary CTX-II, as well as for exploratory bone and cartilage markers of relevance for OA disease (such as sPINP, sBSAP and s(TRAP5b) in blood and NTX-I, CTX-I and αCTX-I in urine). Patients should be fasted overnight (no meals after 11 pm, but water allowed) and restrained from extensive exercise and smoking the previous day. Blood and urine samples will be collected at pre-dose in the morning (between 7-10 am) on each of these visits.

Blood samples (approximately 15 mL) will be taken by venipuncture or cannulation from a forearm vein(s) and collected into serum separator tubes. The samples will be centrifuged, within 1 hour of collection, at 1800g for 10 minutes at room temperature. For each sample the separated serum will be divided into 3 aliquots and transferred into suitably labeled polypropylene tubes and stored within 1.5 hours of collection at at least -70°C until analysis.

The first void of morning urine should have occurred before the urine sample (approximately 10 mL) is taken from a later void. The urine samples will be divided into 3 aliquots into suitably labeled polypropylene tubes. The samples will be stored within 1.5 hours of collection at at least -70°C until analysis.

The date/time of sample collection as well as the date/time of the most recent dose will be collected in the eCRF.

Further details on the provider and handling of the biomarker samples will be provided in the Laboratory Manual.

6.10 Optional Pharmacogenomics Sampling

Blood and urine samples will be collected at visit 2 (baseline) and visit 8 under voluntary ICF for preparation of samples to provide for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics.

Blood samples (approximately 19 mL) will be taken by venipuncture or cannulation from a forearm vein(s) and collected into a DNA PAXgene (approximately 8.5 mL), RNA PAXgene (approximately 2.5 mL) or EDTA tube (approximately 8 mL) for preparation of DNA, RNA and protein, respectively. The DNA and RNA PAXgene tubes will be frozen and stored at at least -70°C until analysis. The EDTA tube will be processed into plasma by centrifugation within 1 hour of collection, at 1500 g for 10 minutes at approximately 4°C. The plasma will be separated into 2 aliquots and transferred into suitably labelled cryovials and stored at at least -70°C until analysis.

A urine sample (approximately 5 mL) will be collected for protein isolation. The urine sample is centrifuged within 1 hour of collection at 1500 g for 5 min at approximately 4°C and the sample is separated into 2 aliquots and transferred into suitably labelled cryovials and stored at at least -70°C until analysis.

6.11 Adverse Events

6.11.1 Definitions of Adverse Events (AEs)

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

All AEs, including undercurrent illnesses, occurring during the study will be documented in the eCRF system. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), must be documented. Worsening of the underlying disease is not considered an AE and should be reported as such only if deemed by the investigator to be beyond the expected progression for OA.

Pre-existing conditions will be recorded in the eCRF system on the Medical History page.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of IMP has been administered.

6.11.2 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.11.2.1 Seriousness

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardise the patient or require intervention to prevent one of the above outcomes.
- Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

6.11.2.2 Intensity

The intensity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the eCRF system:

- Mild: An AE that is easily tolerated and does not interfere with usual activities;
- Moderate: An AE that interferes with usual activities;
- Severe: An AE that prevents usual activities.

6.11.2.3 Causality

The Investigator will assess the causality/relationship between the AE and the IMP as well as the study procedure and record that assessment in the eCRF system.

The causal relationship of the AE to IMP will be described in terms of:

- Related
- Unrelated

6.11.2.4 Adverse Events of Special Interest

No Adverse Events of Special Interest monitoring are applicable for this study.

6.11.2.5 Recording Adverse Events

All AEs and SAEs must be recorded, whether or not considered causally related to the IMP or to the study procedure(s). All AEs and SAEs will be recorded in the eCRF system from the date the Informed Consent Form is signed (visit 1) until the safety follow up visit (visit 9) is completed. All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to IMP, action taken with the IMP, outcome, and whether the event is classified as serious. The information related to the AEs will be captured in the eCRF within the normal data entry timelines.

Whenever feasible, AEs should be documented as medical diagnoses. When AEs do not appear clearly inter-related, individual signs or symptoms may be reported as separate AEs.

6.11.2.6 Reporting Serious Adverse Events

The Investigator will complete the SAE report and will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, sponsor will evaluate the relatedness and expectedness according to the reference document (IB). Based on the Investigator and sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs that occur from the time of signature of informed consent until 4 weeks (visit 9) after the last dose of IMP, whether considered to be associated with the IMP or not, must be reported within 24 hours of awareness to the PAREXEL Safety Contact using the numbers in the List of Study Personnel.

SAEs occurring after the end of the study should be reported to the sponsor by the Investigator, if the Investigator considers there is a causal relationship with the IMP.

The following information is required for an initial report:

- An identifiable reporter (i.e., name, address of Investigator)
- An identifiable patient (i.e., screening/randomization number, but NOT patient name)
- A suspect IMP or clinical study procedure
- A serious adverse event or outcome associated with the use of IMP or clinical study procedure

As far as possible all points on the SAE report form should be covered in the initial report, or the completed SAE form itself must be faxed to the PAREXEL Safety Contact. If important relevant information is missing, PAREXEL will immediately initiate follow-up. The investigator or other site personnel must inform PAREXEL of any follow-up information on a previously reported SAE within 24 hours of when he or she becomes aware of it. The original SAE form must then be sent by mail to the PAREXEL Safety Contact. In addition, the event must be documented in the eCRF system.

In the event that the investigator is unable to enter the SAE in the eCRF or to complete the paper SAE form to report the event within 24 hours of their awareness of the event, the investigator may report the SAE over the telephone via the SAE answering service, and then provide the completed paper SAE form via fax/email. In any case the investigator also has to record the event in the eCRF. If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call utilizing the numbers specified in the list of Study Personnel.

After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. PAREXEL will be responsible for all information processing and reporting according to local legal requirements.

PAREXEL International
Medical Monitor: Francois Burger
Medical hotline: +49 30 30685 274
SAE Fax: +49 30 315118 7777 (24-hour service)
Email: Medical_Berlin@parexel.com

6.11.2.7 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

The sponsor will actively follow-up and collect information on any AE that occurs during the course of a clinical study, however while this activity will continue for any serious AEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

6.11.2.8 Suspected Unexpected Serious Adverse Reactions

Any adverse event that is serious, associated with the use of the IMP, and suspected unexpected serious adverse reaction (SUSAR) has additional reporting requirements, as described below. For the assessment of expectedness, further information is found in the IB section 6 'Summary of Data and Guidance for the investigator.

- If the SUSAR is fatal or life-threatening, associated with the use of the IMP, and unexpected, Regulatory Authorities and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the PAREXEL learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the IMP, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after the PAREXL learns of the event.

The sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The sponsor will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.11.2.9 Pregnancy

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur during study treatment, the patient must be discontinued from the study immediately and the pregnancy must be reported to the sponsor and followed until outcome (completion/termination) of the pregnancy.

Paternal Exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies from the date of the first dose until 6 month after the last dose must be reported to the sponsor and, be followed and documented by completion of the pregnancy report form.

Any pregnancy must be reported to the sponsor according to the SAE reporting procedure whether or not associated with an AE/SAE as described in section 6.11.2.6.

6.11.2.10 Abuse, Misuse, Overdose or Medication Error

Any abuse, misuse, overdose, or medication error must be reported to the sponsor according to the SAE reporting procedure whether or not associated with an AE/SAE as described in section 6.9.2.6.

Note: The 24 hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of IMP when used for a non-medical purpose in a manner that may be detrimental to the individual and/or society.
- Misuse – Intentional use of IMP other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed in this protocol).
- Overdose – Intentional or unintentional intake of a dose of an investigational product exceeding 15% over the total daily mg of MIV-711 as defined in the dosing charts developed per protocol.
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an IMP. Medication errors should be collected/reported for all investigational products under investigation.

The following medication errors are defined as reportable to the sponsor in this study:

- The administration and/or use of the unassigned treatment are always reportable as a medication error.
- The administration and/or use of an expired product should be considered as a reportable medication error.

A blood sample for determination of plasma MIV-711 concentration should be obtained, if at all possible, as soon as possible after Investigator becomes aware of any above, if associated with an AE.

The information related to abuse, misuse, overdose, or medication error will be captured in the eCRF within the normal data entry timelines.

7 STUDY CONDUCT

7.1 Study Schedule

Newly diagnosed and existing patients with symptomatic knee OA consulting their rheumatologist, musculoskeletal physician, orthopaedic surgeon, physiotherapist, or general practitioner will be invited to consent to further contact by the research team. The patient information will be provided and the study will be discussed. Any questions from the patient will be answered. The patient will then have at least 24 hours to discuss the information with whoever they choose. The Screening Phase will last for a maximum of 30 days, during which patients will be checked for eligibility. The clinical laboratory testing will be performed at scheduled visit (Table 1). The patients´ eligibility will be determined by the laboratory results obtained during the screening visit. The study will include 26 weeks of treatment, with patients followed for 30 weeks as per Study Schedule (Table 2).

7.1.1 Screening Visit (Visit 1, Day -30)

The below are the activities at the screening visit which will be documented in eCRF:

- obtaining written informed consent. Study details, risks and benefits will be reviewed and patients will be encouraged to ask questions and clarify any concerns.
- assessing inclusion and exclusion criteria
- obtaining demographic data (including age, gender and race)
- obtaining medical and surgical history
- performing full physical examination
- performing vital signs assessments including weight and height performing 12-lead electrocardiogram assessment
- sampling for urinalysis
- sampling for urine drug screen
- sampling for blood post-menopausal assessments (only post-menopausal or sterile women will be enrolled)
- sampling for blood clinical chemistry and hematology testing
- sampling for blood HBsAg, anti-HBc, HCV, anti-HBs, and HIV testing
- complete NRS (to assess inclusion criterion 1)
- evaluation of existing X-ray (not older than 12 months) of the target knee
- K-L identification of target knee is primarily based on pain, secondarily on K-L grade, and if both sides should be equal with regard to these two criteria, the right knee should always be prioritized
- e-diary dispensing and training
- dispense Patient Emergency Card

7.1.2 Randomisation/Baseline (Visit 2, Day 1)

The below are the activities at the randomization/baseline visit which will be documented in eCRF:

- confirming inclusion and exclusion criteria
- monitoring for AEs, SAEs and concomitant medication
- performing randomization in a 1:1:1 ratio via Interactive Web Response System (IWRS)
- performing full physical examination

- performing vital signs assessments
- performing serial electrocardiogram assessment at pre-dosing, and at 0.5, 1 and 2 h post-dosing
- sampling for urinalysis
- sampling for urinalysis (biomarker)
- sampling for blood clinical chemistry and hematology testing
- sampling for blood biomarker testing
- performing target knee MRI (-7 days)
- NRS, WOMAC, ICOAP
- completing Quality of Life questionnaire: EuroQoLEQ-5D-5L
- dispensing the first IMP at the site. Patient must stay at the clinic for 2 hours after taking the IMP.
- obtaining optional ICF preparation of samples to provide for for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics
- phone call to assess safety and tolerability (completed 5-9 days after the visit)
- e-diary review and training

7.1.3 Safety Visit (Visit 3 [Week 2 ± 2], Visit 4 [Week 4 ± 2] and Visit 7 [Week 20 ± 7 days])

The below are the activities at the safety visits which will be documented in eCRF:

- monitoring for AEs, SAEs and concomitant medication
- performing vital signs assessments
- performing targeted physical examination
- performing 12-lead electrocardiogram assessment 30 minutes post-dose
- sampling for urinalysis
- sampling for urinalysis (biomarker) (at visit 4 only)
- sampling for blood biomarker testing (at visit 4 only)
- sampling for blood clinical chemistry and hematology testing
- sampling for blood PK assessment (at visit 4 only)
- phone call to assess safety and tolerability (completed 5-9 days after the visits)
- dispense IMP at the site (the capsule should be taken from the bottle currently in use by the patient).

7.1.4 Treatment visit (Visit 5 [Week 8 ± 2], Visit 6 [Week 14 ± 7 days], and Visit 8 [Week 26 ± 7 days])

The below are the activities at the treatment visits which will be documented in eCRF:

- monitoring for AEs, SAEs and concomitant medication
- performing vital signs assessments
- measuring weight (at visit 8 only)
- performing full physical examination
- performing 12-lead electrocardiogram assessment
- sampling for urinalysis
- sampling for urinalysis (biomarker) (at visit 6 and visit 8 only)
- sampling for urine drug screen (at visit 5 only)

- sampling for blood clinical chemistry and hematology testing
- sampling for blood PK assessment (at visit 8 only)
- sampling for blood biomarker testing (at visit 6 and visit 8 only)
- performing knee MRI (at visit 8 only)
- completion of NRS, WOMAC, ICOAP, and Global Improvement
- completing Quality of Life questionnaire: EuroQoL EQ-5D-5L (at visit 8 only)
- dispense IMP at the site (the capsule should be taken from the bottle currently in use by the patient)
- drug accountability
- phone call to assess safety and tolerability (completed 5-9 days after the visits, except for visit 8)
- obtaining blood sample for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine sample for proteomics and metabolomics (at visit 8 only)

7.1.5 Safety Follow-up Visit (Visit 9, Week 30 ± 7 days)

The below are the activities at the safety follow-up visit which will be documented in eCRF:

- monitoring for AEs, SAEs and concomitant medication
- performing vital signs assessments
- performing 12-lead electrocardiogram assessment
- sampling for urinalysis
- sampling for urinalysis (biomarker)
- sampling for blood clinical chemistry and hematology testing
- sampling for blood biomarker testing
- delivering NRS for average overall knee pain severity

The end of the study is defined as the last visit 9 (week 30) of the last patient or, if applicable, when the last patient has rolled over to study MIV-711-202 and having finalized visit 2 of that study.

Table 1: Clinical Laboratory Testing

Screening only
Post-menopausal determination: Follicle stimulation hormone (FSH) Female patients **must** be of non-childbearing potential either as naturally (spontaneously) post-menopausal or due to hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy (as determined by patient medical history). Naturally (spontaneously) post-menopausal is defined as being amenorrhoic for 12 months without an alternative medical cause and with a screening follicle stimulating hormone indicating post-menopausal state.
Fasting samples are required at all study visits as fasting glucose is required as part of the chemistry samples.
Hematology: WBC and differential, % and absolute for: neutrophils, lymphocytes, monocytes, eosinophils, basophils; hemoglobin, hematocrit, RBC, RBC indices (MCV, MCH and MCHC) and morphology, platelet count
Chemistry: urea nitrogen, creatinine, calcium, sodium, potassium, bicarbonate, chloride, total protein, fasting glucose, total bilirubin, direct bilirubin and indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, CPK, CRP (at screening only)

Urinalysis: with microscopic: specific gravity, pH , protein, glucose, ketones, nitrites, blood and leukocyte esterase
Urine Drug Screen: Amphetamine, Benzodiazepines, THC, Cocaine, Oxycodone and Opiate **Hepatitis B surface antigen, total Hepatitis B Core antibodies, antibodies to Hepatitis B Surface antigen, Hepatitis C virus, HIV 1/2** **PTH (parathyroid hormone)**

The above parameters will be analysed by a central laboratory. Total blood volumes to be collected are detailed in Appendix 1. Further details on the provider and handling of laboratory samples will be provided in the Laboratory Manual.

The study schedule is summarised in Table 2.

Table 2: Study Schedule

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Weeks	**-4**	**1**	**2**	**4**	**8**	**14**	**20**	**26**	**30**
Day	**up to 30 days**	**Day 1**	**day 15 ±2 days**	**day 29 ±2 days**	**day 57 ±2 days**	**±7 days**	**±7 days**	**±7 days**	**± 7 days**
Visit Description	**Screening**	**Randomisation /Baseline**	**Treatment period**						**Safety follow-up**
Signed informed consent	X								
Randomisation		X							
Inclusion/exclusion criteria	X	X							
Target knee identification[A]	X								
Demographics	X								
Weight	X							X	
Height	X								
Medical & Surgical history	X								
Physical examination	X	X	X[B]	X[B]	X	X	X[B]	X	
Vital signs, including body temperature	X	X	X	X	X	X	X	X	X
12-Lead ECG[C]	X	X	X	X	X	X	X	X	X
Clinical chemistry/ Haematology	X	X	X	X	X	X	X	X	X
Urinalysis[D]	X	X	X	X	X	X	X	X	X
Urine drug screen	X				X				
Post-menopausal assessment (females only)	X								

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Weeks	**-4**	**1**	**2**	**4**	**8**	**14**	**20**	**26**	**30**
Day	**up to 30 days**	**Day 1**	**day 15 ±2 days**	**day 29 ±2 days**	**day 57 ±2 days**	**±7 days**	**±7 days**	**±7 days**	**± 7 days**
Visit Description	**Screening**	**Randomisation /Baseline**	**Treatment period**						**Safety follow-up**
HBsAg, anti-HBc, anti-HBs, HCV, and HIV test	X								
e-diary dispensing and training	X								
Patient Emergency Card dispense	X								
MRI of target knee[E]		X						X	
e-diary for pain and analgesic[F]		X				X		X	
Duration and onset of knee pain		X							
NRS, ICOAP, WOMAC	X[G]	X			X	X		X	X[G]
Global improvement (6-point Likert scale)					X	X		X	
EuroQoL EQ-5D-5L		X						X	
Brief Medication Questionnaire					X	X		X	
Dispense IMP[I]		X[H]			X	X			
Drug accountability		X			X	X		X	
PK sampling (blood)				X				X	

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Weeks	**-4**	**1**	**2**	**4**	**8**	**14**	**20**	**26**	**30**
Day	**up to 30 days**	**Day 1**	**day 15 ±2 days**	**day 29 ±2 days**	**day 57 ±2 days**	**±7 days**	**±7 days**	**±7 days**	**± 7 days**
Visit Description	**Screening**	**Randomisation /Baseline**	**Treatment period**						**Safety follow-up**
Biomarker samples[J]		X		X		X		X	X
AEs/SAEs monitoring	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X
Phone call to assess safety and tolerability[K]		X	X	X	X	X	X		
Blood sample for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine sample for proteomics and metabolomics[L]		X						X	

A) Selection of target knee is primarily based on pain, secondarily on K-L grade, and if both sides should be equal with regard to these two criteria, the right knee should always be prioritized.
B) Targeted physical examination. Full physical examination at all other visits.
C) At visit 2 at pre-dosing, 0.5, 1 and 2 h post dosing (± 10 minutes). At all other visits 30 minutes post-dose (± 10 minutes).
D) If urinalysis is positive for blood, nitrites, leukocyte esterase, and/or protein, additional microscopic analysis may be performed.
E) MRI should be performed at visit 2 (- 7 days) and at visit 8 (± 5 days).
F) To be completed at home during the 2 weeks prior to the marked visit.
G) Only NRS for average overall knee pain severity (1 week recall) for both knees
H) The first dose of IMP will be dispensed to the patient at the site. Date and time should be recorded in the eCRF. The first dose should be given to the patient after all baseline assessments has been performed including completion of PROs. Patients take the IMP in the clinic in a fasting state and must stay at the clinic for 2 hours after intake of the IMP.
I) Patients take IMP in the clinic in a fasting state. Breakfast can be eaten 1 hour after IMP intake. The last dose of the IMP will be taken at the site during visit 8.
J) Both blood and urine sample will be collected for biomarker. The first void of morning urine should have occurred before the urine sample is taken from a later void. The patients must be fasting when all biomarker samples are taken.
K) The phone call should be made 5-9 days after all dosing visits.
L) Blood will be collected for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine will be collected for proteomics and metabolomics pre-dose

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Weeks	**-4**	**1**	**2**	**4**	**8**	**14**	**20**	**26**	**30**
Day	**up to 30 days**	**Day 1**	**day 15 ±2 days**	**day 29 ±2 days**	**day 57 ±2 days**	**±7 days**	**±7 days**	**±7 days**	**± 7 days**
Visit Description	**Screening**	**Randomisation /Baseline**	**Treatment period**						**Safety follow-up**

at Visit 8 from patients who provide additional written consent.

7.2 Early Termination Visit

All patients who discontinue the IMP because of an AE, or for any other reason, will be asked to complete the safety follow-up visit (visit 9) as outlined in the study schedule (Table 2).

In addition to the assessments described in Section 7.1.5, the following should also be completed:

- drug accountability
- return of eDiary
- physical examination
- performing knee MRI (±5 days) (if withdrawal is after visit 6)
- obtaining optional blood samples for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine samples for proteomics and lipidomics.

7.3 Discontinuation of the study

No formal interim analysis to allow early stopping of the study on the basis of demonstrating efficacy or futility is planned.

The study will be monitored by the independent Data Monitoring and Ethics Committee (DMEC). Any serious adverse event will be reported to the committee who may recommend stopping the study for safety reasons. Interim safety analyses (i.e. no efficacy analyses) will be undertaken after 50, 100, 150 and 200 patients have completed the visit 6. No formal statistical tests will be undertaken but adverse events will be summarised and tabulated for each group separately. If, in the view of the DMEC, the number or severity of adverse events in one of the groups is of concern, consideration will be given to the future conduct and design of the study, and to whether further formal interim analyses are required.

The study will be discontinued due to events such as exemplified below:

- The Sponsor (following DMEC recommendation or in absence of such recommendation) judges it necessary for medical, safety, regulatory or any other reasons consistent with applicable laws, regulations and GCP.
- If SAEs are assessed as causally related to IMP or in presence of other significant medical events as judged by the sponsor
- New information leading to unfavorable risk-benefit judgment of the IMP, as judged by the investigator and/or sponsor, e.g., due to:
    1) Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
    2) Other unfavorable safety findings.
- If events are not considered to be consistent with continuation of the study.
- Poor enrolment of patients making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the sponsor’s IMP.

8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

Before unblinding and database lock, a separate SAP will be finalised, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

8.1 Study Patients

8.1.1 Disposition of Patients

The number and percentage of patients entering and completing each phase of the study will be presented, stratified by treatment. Reasons for withdrawal pre--and post-randomization will also be summarized.

The disposition of patients will also include information on the number and percentage of patients who:

- completed IMP and follow-up,
- withdrew from IMP but completed follow-up,
- withdrew from IMP and from follow-up.

8.1.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the sponsor. Major deviations from the protocol will lead to the exclusion of a patient from the Per Protocol Set (PPS). Deviations will be defined prior to unblinding.

8.1.3 Analysis Set

- The Intention-to-Treat population (ITT): all randomised patients in the treatment group to which they were randomised, regardless of whether treatment was received as planned.
- The full analysis set (modified ITT approach; mITT): all patients having both a baseline and at least one post-baseline value for the primary variable (NRS pain score).
- PPS: those patients who adhered to the treatment regimen of the program to which they were allocated, provided sufficient assessment of primary outcomes, and did not violate the study protocol in any substantial way.

Major protocol violators and exclusions from the per-protocol set will be identified by a panel, including the clinical project manager, study statistician, and other appropriate clinical study team members.

The following criteria will be used to exclude a patient from the per-protocol set:

- Incorrect diagnosis
- Arthroscopy in the target knee during the study period
- Missing more than 5 doses of MIV-711

The panel will review these criteria using blinded data prior to data analysis.

- The safety analysis set (SAF): all patients receiving at least one dose of either MIV-711 or placebo, analysed according to treatment actually received.

The primary and secondary efficacy analysis will be based on mITT and PPS, to assess the sensitivity of the analysis to the choice of analysis set. All safety analyses will be based upon the SAF.

Demographic and baseline characteristics will be evaluated for the ITT and for the PPS. If one or more patients received incorrect IMP, these data will also be presented for the SAF.

8.2 General Consideration

All statistical tests will be one-sided and will be performed at the 5% level of significance (Type I error α=0.05).

Continuous data will be summarised by treatment group using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percents).

Analysis and data conventions:

Definition of baseline

The baseline assessment to be used for calculating change from baseline will be the last valid assessment prior to first dose administration.

Visit windows

Assessments taken outside of protocol allowable windows will be displayed according to the eCRF assessment recorded by the investigator.

Unscheduled assessments

Extra (repeat) assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in data listings.

For repeat/unscheduled assessments collected prior to first dose administration, the last assessment taken for a time point will be used in data summaries (summary tables, figures, and statistical analysis). For repeat/unscheduled collected after the first dose administration the original assessment for any given time point will be used in the data summaries (summary tables, figures, and statistical analysis).

It is noted that invalid laboratory data may not be used (from hemolysed samples, mishandled samples, quantity not sufficient or other conditions that would render values invalid).

Missing data conventions

In general, data will not be imputed for safety analysis. Efficacy analysis imputations will use last observation carried forward (LOCF) for patients in analysis populations as described. Additional details will be in the SAP.

Any outliers that are detected during the blind review of the data will be investigated. If necessary, queries will be issued to the Investigator to either correct or confirm the outlier.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant disease, and concomitant medication will be summarised by means of descriptive statistics (n, mean, SD, median, minimum and maximum) or frequency tables, overall and stratified by treatment.

8.4 Treatment Compliance

Treatment compliance as measured in Section 5.6 will be summarised by means of descriptive statistics (n, mean, SD, median, minimum, and maximum) and/or frequency tables and stratified by treatment.

8.5 Statistical Methodology

8.5.1 Hypothesis to be Tested

The primary hypothesis of this study is that MIV-711 will reduce pain in patients with moderate knee osteoarthritis diagnosed based on symptomatic and radiologic criteria.

8.5.2 Efficacy

8.5.2.1 Statistical Methodology for Primary Efficacy Endpoints

In order to test the hypothesis, the change from baseline in NRS pain score will be analysed using a linear mixed model using the FAS (mITT). Only post-baseline NRS values will be used as dependent variable. Baseline NRS will be included as a covariate. The model will include fixed effects for treatment group, baseline value, chronic analgesic use minimization factors, week and week-by-treatment group interaction; site will be modeled as a random effect.

The contrast of primary interest will be the treatment difference at visit 8. Least Square means (LSmeans) at visit 8 for the change from baseline score will be reported from the mixed model. LSmeans for the overall effect of treatment, estimates of the pair-wise treatment differences, two-sided 95% confidence intervals (CI), and p-value (one-sided) will be provided.

Development over time will be summarised by graphs of LSmeans and 95%-confidence limits as appropriate.

As a sensitivity analysis, the primary endpoint will also be analysed by using the PP subset, following the same conventions as in the primary analysis on the FAS population.

8.5.2.2 Statistical Methodology for Secondary Efficacy Endpoints

All secondary endpoints will be analysed using the same statistical model specified for the primary endpoint, adjusting for the same factors as the primary analysis. The mITT population will be used for all secondary analyses.

Some secondary endpoints such as QoL will be obtained at visit 2 (baseline) and visit 8 only. In the analysis of biomarkers that are sampled at multiple visits, all sampled time points will be considered for change from baseline and comparison to placebo in the respective cases.

For all outcomes distributional assumptions will be checked using examination of empirical distributions and model residuals. If necessary, data will be transformed prior to analysis if this improves the model fit, or normalises the distribution of the residuals. Non-parametric methods may be applied if appropriate.

For the analysis of all primary and secondary efficacy endpoints, alternate statistical methods maybe considered that will include the use of generalised linear models that account for the response variable having a “non-normal” distribution. Additional details will be provided in the SAP.

All secondary outcomes will be summarised descriptively (mean, SD, median, minimum and maximum for continuous data and counts and percentages for categorical data).

No subgroup analyses are planned in this Phase IIa study.

No interim analysis will be conducted for any efficacy endpoint.

An unblinded interim safety analysis will be conducted after 50, 100, 150 and 200 patients have completed the visit 6. No formal statistical tests will be undertaken. Adverse events will be summarised descriptively and tabulated by treatment group (see section 8.6). The DMEC will consider the results of the AE summaries when making decisions regarding dosing of

subsequent cohorts (i.e. need for dose stoppages) or the need for formal interm analysis of non-safety data.

8.5.2.3 Statistical Methodology for Exploratory Endpoints

The exploratory analysis of additional bone and cartilage biomarkers, imaging and PK assessments are not part of the statistical analysis set, and may therefore be listed and summarised using descriptive statistics only or presented in separate reports. The pharmacokinetic measurements in this study will be performed using sparse sampling in which the date/time of sample collection as well as the date/time of the most recent dose will be collected in the eCRF to allow for a future population pharmacokinetic analysis of these data. For the purpose of this study, the plasma concentrations of parent and metabolite forms of MIV-711 will be an additional exploratory endpoint and will be reported as outlined above. Any subsequent analysis of the biomarker samples stored will not be part of the present study reporting.

8.5.3 Safety

There will be no formal statistical hypothesis testing for safety data in this study, therefore only summary statistics will be provided. Safety summaries will be presented by treatment group and scheduled assessment for the SAF. Summary statistics (number of observations, mean, SD, median, minimum and maximum values) will be presented by treatment group for continuous variables, and number and percentages (n, %) will be presented by treatment group for categorical variables. Where applicable, changes from baseline will also be summarised for each treatment group.

Treatment-emergent adverse events will be summarised by preferred term and system organ class and classified according to the latest version of coded Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of TEAEs will be summarised by system organ class, preferred term and treatment group in the SAF. Treatment-emergent adverse events will be further summarised by treatment group with respect to severity and relationship to IMP. Treatment-emergent adverse events related to IMP, leading to withdrawal, serious TEAEs, and deaths will be summarised by treatment group.

Clinical laboratory tests (hematology, serum chemistry, ECG, and vital signs) will be summarised by treatment group for the SAF at each scheduled assessment. Potentially clinically important findings will also be summarised by treatment group and listed.

The number of patients taking rescue medication, the amount of rescue medication taken and the reason for use will be tabulated and summarised descriptively by treatment.

8.6 Interim Analyses

No formal interim analysis to allow early stopping of the study on the basis of demonstrating efficacy or futility is planned. Unblinded Interim safety analyses (i.e. no efficacy analyses) will be undertaken after 50, 100, 150 and 200 patients have completed visit 6.

8.7 Sample Size and Sample Size Calculation

8.7.1 Primary Endpoint consideration

The sample size is based on the primary efficacy outcome of change in pain score from baseline, measured using the 0-10 numerical rating score and comparing MIV-711 and placebo groups. The following were input to the calculation.

- A clinically important effect for changes in chronic musculoskeletal pain severity has been estimated as 1.0 point. [59]

- The between-patient SD for change in pain score of 2.256 was obtained from a review of the literature of clinical studies in patients with knee OA. This was the average SD reported in a large study of similar patients assessed at 12 months after treatment. [60]
- Using a Bayesian decision-theoretic approach Stallard recommended that operating characteristics for Phase IIa studies can be relaxed with maximum (one-sided) type I and type II errors of 0.2 and 0.4 respectively.[61] For this study a stricter approach was considered requiring the power of the test to be at least 80% and the one-sided type I error rate to be fixed at 0.05
- Loss to follow-up is expected to be 20% at by visit 8.

Based upon the assumptions above we require a sample size of 80 patients per group, or 240 patients in total, with 192 patients providing the primary outcome measurement at visit 8.

Statistical analysis will be carried out using mITT and per-protocol populations. All data analysis and statistical programming will be conducted using the SAS software (Version 9.1 or higher). Significance tests will be one-sided at the 5% level (Type I error α=0.05).

For the primary endpoint, change from visit 2 (baseline) to visit 8 in NRS pain score, the type I error for the tests of the two doses will be protected by performing a fixed-sequence multiple-testing procedure. The order of steps is defined below:

1. 200 mg versus placebo
2. 100 mg versus placebo

To adjust for the multiple testing of two doses, the second step will only be considered as confirmatory providing the previous step is successful at one-sided 5%-level ($p<0.05$). If the previous step is not successful, the analysis of the following step will be considered descriptive.

The study will be blinded until the final analysis.

8.7.2 Key Secondary Endpoint power consideration

The sample size is based on the change of bone area (mm^2) of the medial femoral (MF) condyle from baseline, which was found to be the most responsive region in a study of bone area.[23]

The following were input to the calculation.

- In a comparable group of patients within an observational clinical study, the mean change found in MF area was 13.5mm^2 in 6 months
- Standard deviation for change in MF bone area over 6 months for this study was 16.0 mm^2
- With the present trial design we will have 80% power to detect an improvement in bone surface area of the order of 0.45 (between-patient) SD, with a 1-sided significance of 5% and allowing for 20% loss to follow up. This equates to 7.2mm^2 of change in area, approximately half of the expected bone area change in 6 months (13.5mm^2)

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

This study will be conducted according to the protocol, European Union clinical trial directive (2001/20/EC), ICH E6 (R1), GCP guidelines, and applicable local or regional regulatory requirements.

9.1 Data Quality Assurance

PAREXEL will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate source documents designed to record all observations and other data pertinent to the study for each study patient. All information recorded on the eCRF system for this study must be consistent with the patients' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data centre, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible CRA or data manger will raise a query in the eCRF application (DataLabs). The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the CRA will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in an eCRF completion guideline. In addition, site personnel will receive training on the eCRF.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the EDC system promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG, MRI scans, and X-rays.

The original eCRF entries for each patient will be checked against source documents at the study site by the CRA.

9.2.1 Data collection

The Investigators (and appropriately authorised staff) will be given access to an online web−based eCRF) system called DataLabs which is 21 CFR Part 11 compliant. DataLabs is specifically designed for the collection of the clinical data in electronic format. Access and right to the eCRF system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the investigator and authorised staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be

completed as soon as possible during or immediately after the patient's visit or assessment. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerised data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on−line directly by the Investigator or by authorised staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the investigator will be required to electronically sign off the clinical data

9.3 Access to Source Data

During the study, a CRA will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to CRA the progress of the study. Moreover, Regulatory Authorities of certain countries, IECs, and/or the sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit or inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures PAREXEL and the sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into the eCRF (as detailed in Section 9.2.1).

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the MedDRA) terminology.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

9.5 Data Monitoring

A Trial Steering Committee (TSC) will be established and will be blinded and responsible for providing overall supervision for the study in accordance with pre-agreed terms of reference, in particular to the progress of the study, adherence to the protocol and patient safety. Operationally this will include consultation regarding the study design, subsequent amendments and emerging data and research relevant to the study, including open DMEC reports and the results of other research that may have a direct bearing on the future conduct of the study. They will also ensure that any action taken protects the rights, safety and wellbeing of patients and the study is conducted to the rigorous standards of GCP. It is anticipated that the TSC will meet at approximately 6-12 monthly intervals and after each independent DMEC review as required. Any SAE will be reported to the DMEC who may recommend stopping the study for safety reasons. Interim safety analyses (i.e. no efficacy analyses) will be undertaken after 50, 100, 150 and 200 patients have completed visit 6.

The independent DMEC will be set up to monitor study safety which will be specified in a DMEC charter. The independent DMEC will be unblinded and include an independent chair having specialist osteoarthritis expertise and experience of studies in this area, an independent

statistician and one other member will also be appointed. Specifically they will monitor AEs and serious SAEs) related to the treatments received in accordance with the recommendations of performing a clinical study of an IMP. In addition the independent DMEC will make recommendations on continuation of the study based on interim safety analyses.

9.6 Safety Monitoring Plan

A change in the value of a clinical laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EOT with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

9.7 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 10 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

No essential documents may be destroyed without prior written approval from the sponsor.

9.8 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, and of the Declaration of Helsinki (1996). The study also will be carried out in accordance with local legal requirements.

9.9 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF system.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

9.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/Competent Authorities, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/Competent Authority approval prior to implementation (if appropriate). Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.11 Duration of the Study

The study will be conducted from November 2015 to 31 March 2017.

9.12 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating patients must be maintained. Patients will be identified in the eCRF system and other documents submitted to PAREXEL by their patient number and date of birth, not by name. Documents that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator and should never be submitted to PAREXEL or the Sponsor.

9.13 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IRB/IECs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.14 Liability and Insurance

The sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.15 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the sponsor in advance. Details are provided in a separate document.

10 REFERENCE LIST

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11 APPENDICES

11.1 APPENDIX 1, Total Blood Volumes

The total volume of blood that will be drawn from each patient in this study is as follows:

Assessment	Sample Volume (mL)	No of samples	Total Volume (mL)
Safety • Clinical chemistry • Haematology	 9.5 2	 9 9	 85.5 18
Pharmacokinetic samples	5	6	30
Pharmacogenetic samples	19	2	38
Hepatitis B and C, HIV test, anti-HBs test, and anti-HBc test	3	1	3
Biomarker analysis	15	5	75
Additional unforeseeable samples			50.5
Total			**300.0**