An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with 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.
Principal/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
Sponsor Protocol No.:	MIV-711-202
EudraCT No.:	2016-001096-73
Study Drug Name:	MIV-711
Development Phase:	Phase II
Date of Protocol:	01 July 2016

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: An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with 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

01-Jul-2016
Date

Declaration of the National Coordinating Investigator

Title: An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with 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.

National Coordinating Investigator

Signature Date

PHILIP CONAGHAN

Name (block letters)

PROFESSOR

Title (block letters)

LEEDS INSTITUTE OF RHEUMATIC AND MUSCULOSKELETAL MEDICINE

Institution (block letters)

UNITED KINGDOM

Country

Declaration of the Investigator

Title: An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with 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), patient 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 patients.

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 centre

Signature Date

Name (block letters)

Title (block letters)

Institution (block letters)

Country

PROTOCOL SYNOPSIS

Title	An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with Knee Joint Osteoarthritis
Sponsor Study No.	MIV-711-202
Phase	Phase II
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	Five sites distributed in 5 European countries. 1) PAREXEL Berlin Early Phase Clinical Unit, PAREXEL International GmbH, Spandauer Damm 130, 14050 Berlin, Germany 2) MC Comac Medical, 13 Urvich Str, 1612 Sofia, Bulgaria 3) LLC ARENSIA Exploratory Medicine, Research Institute of Clinical Medicine, 13a, Tevdore Mgvdeli Str. 0112 Tbilisi, Georgia 4) LLC ARENSIA Exploratory Medicine, Republican Clinical Hospital, 29 Testemitanu Str. 2025 Chisinau, Republic of Moldova 5) SC ARENSIA Exploratory Medicine SRL Spitalul Clinic Colentina, Sectia de Medicina Interna III, Sos. Stefan cel Mare Nr. 19-21, Sector 2 Bucharest 020125, Romania
Objective	The primary objective is to assess the safety and tolerability of 200 mg MIV-711 q.d. over 52 (26+26) weeks in patients with symptomatic and radiographic knee osteoarthritis (OA).

Design

This is a multicentre, open-label, one-arm Phase II extension study to evaluate the safety and tolerability of MIV-711 for up to 52 (26+26) weeks in patients with knee joint OA. Patients to be enrolled will be selected from the patients in Study MIV-711-201 (a randomised, double-blind, placebo-controlled Phase IIa study to evaluate efficacy, safety and tolerability of MIV-711 in knee joint osteoarthritis).

Patients treated with 200 mg MIV-711 once daily (q.d.) in Study MIV-711-201 whose symptoms did not clinically significantly deteriorate as defined by a numeric rating scale (NRS) increase of ≤ 2 compared to Baseline will be offered to roll over for 26 weeks' extended treatment primarily evaluating longer term safety and tolerability. The 52 (26+26) weeks total treatment also allows for a more suitable treatment length for the exploratory study of any structural effects of MIV-711 on joint cartilage thickness. In this protocol, this population is referred to as Study Population A.

The second objective of this study is the exploratory assessment of the treatment effect in a

group of OA patients that has confirmed symptom progression over the last 6 months. This means that patients receiving placebo in Study MIV-711-201 and that had experienced a clinical worsening as defined by increased NRS versus Baseline of ≥2 will be offered to receive 200 mg MIV-711 q.d. for the next 6 months. In this protocol, this population is referred to as Study Population B. The safety and tolerability in Study Population B constitutes a secondary objective whereas all other analyses are exploratory.

All patients in Study MIV-711-201 (Eudract No. 2015-003230-26) at the participating sites included in Study MIV-711-202 will be given the opportunity to participate provided that they meet the eligibility criteria.

To ensure the patients will have sufficient time to consider their participation in the study the informed consent form will be given to the patients prior to Visit 8 in Study MIV-711-201. Visit 8 of Study MIV-711-201 will ideally be conducted on the same day as Visit 1 of the present study. If these visits are conducted on the same day, the results of the following assessments will be recorded in the electronic case report form (eCRF) for both studies; urine and blood sampling for safety, vital signs, physical examination and electrocardiogram (ECG).

A central person, independent from the study, with access to the randomisation list and the eCRF for the MIV-711-201 study will confirm Inclusion Criterion 1. The confirmation will be communicated to the site staff and the study team via fax/email without revealing the treatment in MIV-711-201 or the change in NRS score.

All enrolled patients will receive 200 mg q.d. oral dose of MIV-711 for 26 weeks in addition to their current medication. MIV-711 200 mg will be provided as identical capsules to those used in Study MIV-711-201.

The patients will take the last dose of IMP in Study MIV-711-201 at Visit 8 and dosing in the present study will be started at Visit 2 after a screening period of 10±5 days.

Patients who are not eligible to participate in the present study will return for the safety follow up visit (Visit 9) in Study MIV-711-201.

Patients will be permitted to remain on their current analgesic regimen with any changes in concomitant medications reported and recorded at study visits as well as in a patient-reported daily e-diary for two 2-week periods prior to Visit 4 and Visit 5.

The study consists of a Screening period of approximately 2 weeks (Visit 1), eligibility at Visit 2, an open-label treatment period of 26 weeks from Visit 2 through Visit 5, and a follow-up period of 4 weeks (Visit 6) after the last dose of study treatment is administered. Telephone calls will be made 5-9 days after all dosing visits for safety and tolerability. There will be additional phone calls at Week 10 and Week 20 for safety and tolerability.

A Data Monitoring and Ethics Committee will meet to review the unblinded safety and tolerability data after the first 25 patients complete Visit 4 and Visit 5.

Treatment	All patients will receive a 200 mg oral dose of MIV-711 q.d. for 26 weeks in addition to their current medication.
Number of Patients	All patients in Study MIV-711-201 at the participating sites included in Study MIV-711-202 will be given the opportunity to participate provided that they meet the eligibility criteria. However, based on the inclusion and exclusion criteria it is anticipated that 50-80 patients will be eligible for participation. The patients will be recruited from up to 5 centres in up to 5 countries for this study.
Population	The study population will consist of patients with symptomatic and radiographic knee joint OA who have participated in Study MIV-711-201. Patients must be able to provide written consent, be

	approved by the investigator for eligibility as well as meeting all the inclusion criteria and none of the exclusion criteria.

Criteria for inclusion and exclusion

Inclusion:

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

1. Previously enrolled in the MIV-711-201 study including completion of Visit 8 either by

   - Receiving MIV-711 200 mg and had non-significant clinical worsening on the primary endpoint as defined by NRS increase of ≤2

   OR by

   - Receiving placebo and had a clinically significant worsening on the primary endpoint as defined by NRS increase of ≥2

   The NRS result will be derived using the primary endpoint from Study MIV-711-201: NRS average knee pain in the target knee with 7 days recall: increase from Baseline (Visit 2 of Study MIV-711-201) to Visit 8 of Study MIV-711-201.

2. 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 amenorrhoeic for 12 months without an alternative medical cause and with a Screening follicle stimulating hormone test indicating post-menopausal state.

3. 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).

4. The patient's usual analgesic regimen (in case of use) should remain the same as for Visit 8 in the MIV-711-201 study (i.e., Visit 1 in the MIV-711-202 study).

   NOTE: 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 during his/her participation in the study, then this will be allowed and should be properly documented in the patient file and the eCRF.

5. Needs to be able to communicate well with the investigators and staff.

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

Exclusion:

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. Ongoing or a history of atrial fibrillation.
4. Currently receiving medication that affects cartilage or bone metabolism (other than study drug; hormone replacement therapy taken for more than 6 months is allowed).
5. Current or recurrent disease that could affect the action, absorption or disposition of MIV-711, or could affect clinical assessments or clinical laboratory assessments.
6. 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.
7. Any medical condition, adverse event (AE), clinical or laboratory finding from Study MIV-711-201 that, in the opinion of the Investigator, would preclude inclusion in the present clinical study.
8. Known or suspected intolerance or hypersensitivity to the investigational medicinal product, closely related compounds, or any of the stated ingredients.
9. History of alcohol or other substance abuse within the last year.
10. Use of an investigational product other than MIV-711 during participation in the MIV-711-201 study and /or active enrolment in another drug or vaccine clinical study.
11. Significant target knee injury or surgery during participation in the MIV-711-201 study.
12. 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.
13. 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 venepuncture or lack of adequate venous access for required blood sampling during the study period).
14. Use of intra-articular hyaluronic acid in the target knee during participation in the MIV-711-201 study.
15. Use of intra-articular, intra-muscular or oral corticosteroids during participation in the MIV-711-201 study.
16. Commencement of non-pharmacological OA interventions during participation in the MIV-711-201 study.
17. 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.
18. Lack of MRI of the knee from Visit 8 in the MIV-711-201 study due to special circumstances, such as claustrophobia or difficulties to fit the knee coil.
19. Patients with contra-indication to MRI of the knee.

Outcome variables

Safety:

The primary outcome variables for this study are related to safety:

- Incidence and severity of adverse events
- Incidence and severity of clinical laboratory abnormalities
- Physical examination findings by the patient
- Incidence and severity of ECG abnormalities
- Mean change from Baseline (Visit 2 of Study MIV-711-201) in vital signs (blood pressure, heart rate, temperature) and oxygen saturation
- Categorical summary of observed vital signs and vital sign changes compared to Baseline (Visit 2 of Study MIV-711-201), by patient

Efficacy:

The secondary outcome variables are related to efficacy:

- The effect of MIV-711 on MRI cartilage thickness loss
- The effect of MIV-711 on MRI bone marrow lesion volume
- The effect of MIV-711 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- To assess the effect of MIV-711 on MRI knee joint bone area.

Note: all MRI assessments refer to the target knee unless stated otherwise.

Exploratory outcome variables:

- 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 patient reported e-diary daily recall knee joint pain
- The effect of MIV-711 on patient reported e-diary daily recall analgesics use
- Serum and urinary biomarkers (C-terminal telopeptide of collagen type I [CTX-I], procollagen type I N-terminal propeptide [PINP], bone specific alkaline phosphatase [BSAP], C-terminal telopeptide of collagen type II [CTX-II], N-terminal telopeptide of collagen type I [NTX-I], αCTX-I and tartrate-resistant acid phosphatase 5b [TRAP5b])
- Compound index of MRI bone area and cartilage volume
- Pharmacokinetics: MIV-711 Pharmacokinetic (PK) parameters and their relationship to covariates such as age, weight, gender, liver function and concomitant medications.

All of the above denoted secondary and exploratory parameters are considered as exploratory objectives in Study Population B and will be evaluated over 26 weeks.

Statistical Methods

Primary Analysis

The primary outcome will be to study the safety and tolerability of MIV-711 in OA patients who have received treatment for up to 52 (26+26) weeks. Safety and tolerability will be assessed descriptively in summary tables presented over time. All data presentations addressing the primary outcome will use Study Population A.

Secondary Analysis

For Study Population B, the safety and tolerability of 200 mg MIV-711 will be studied for 26 weeks. Safety and tolerability will be assessed descriptively in summary tables presented over time.

All other secondary analyses will be undertaken using Study Population A while they will be undertaken as exploratory analyses on Study Population B.

For Study Population A all secondary outcome variables will be analysed using descriptive summary tables presenting statistics for, number of non-missing values means, medians, standard deviations, minimum and maximum values. Frequency tables (counts and percentages) will be presented in tables where appropriate. Figures of secondary response over time will be presented as appropriate.

For all outcome variables analysed using a linear model, 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 secondary 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 Statistical Analysis Plan.

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

No comparisons between Study Populations A and B will be undertaken.

Exploratory Analysis

The exploratory analysis of patient-reported outcomes, bone and cartilage biomarkers, MRI imaging and PK assessments will 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 potential metabolites of MIV-711 will be an additional exploratory endpoint and will be reported as outlined above. In the analysis of biomarkers that are sampled at multiple visits, all sampled time points will be considered for change from Baseline in the respective cases. In applicable cases PK and biomarker data may be analysed using area under the curve calculations.

LIST OF STUDY PERSONNEL

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
Contract Research Organization	PAREXEL International (IRL) Limited, 70 Sir John Rogerson's Quay, Dublin 2, Ireland.
Adverse Event Reporting	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
Central Imaging Reader	Imorphics Kilburn House, Lloyd Street North, Manchester Science Park, Manchester M15 6SE,United Kingdom
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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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

α CTX-I	α C-terminal telopeptide of collagen type I
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24h}	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
DMOAD	Disease modifying OA drug
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
ECG	Electrocardiogram
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
FTIM	First time in man
FSE	Fast spin echo
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's brochure
ICF	Informed consent form
ICOAP	Intermittent and constant osteoarthritis pain
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRT	Interactive Response Technology
IWRS	Interactive Web Response System

LSmeans	Least square means
MedDRA	Medical Dictionary for Regulatory Activities
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
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PD	Proton density
PINP	Procollagen type I N-terminal propeptide
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported outcomes
q.d.	Once daily
QoL	Quality of Life
QTcF	QTc interval (Fridericia's correction)
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard Deviation
PINP	Procollagen type I N-terminal propeptide
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
TRAP5b	Tartrate-resistant acid phosphatase 5b
TSC	Trial Steering Committee
ULN	Upper limit of normal
UV	Ultra violet

WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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. One Phase I study with MIV-711 is completed and a three-arm, 240 patient, 6 month, Phase IIa, randomised, placebo-controlled study to assess the efficacy of MIV-711 in treating painful, radiographic knee OA, both in terms of symptoms and structural progression is currently in progress. The present protocol details the intention to conduct an extension of the ongoing Phase IIa study. The purpose is to establish 52 weeks safety and tolerability data in a subset of the study population.

2 INTRODUCTION

2.1 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 typically 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 cartilage 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. [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 2.2, Section 2.4 and Section 2.5), 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 included in the Investigator's Brochure (IB).

2.2 Pharmacokinetic, Pharmacodynamic and Safety results from MIV-711 First Time in Man Study and Blinded Safety and Tolerability Summary from MIV-711-201

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 (q.d.) for 7 days and in healthy post-menopausal female volunteers at multiple doses of 100 mg q.d. for 28 days. The single dose part enrolled 18 males and 9 females with an age range of 19-64 years. The multiple dose parts enrolled 15 males and 24 females with an age range of 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 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 q.d. for 7 days or 100 mg q.d. 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 (for further details see Section 2.4, Section 2.5 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 per protocol ECG to have asymptomatic atrial fibrillation after 3 q.d. 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.

The ongoing MIV-711-201 study, from which the patients in the current protocol will be recruited, will include 240 patients under 1:1:1 randomisation to placebo: 100 mg MIV-711: 200 mg MIV-711. The first patient was randomised in March 2016 and recruitment is ongoing; as of 21 June 2016, 102 patients have been enrolled. No treatment-related serious adverse events (SAEs) have been reported to date. One unrelated SAE was reported before the start of dosing. Seven patients were withdrawn from the study due to the following reasons: increased liver function tests; severe polymyalgia; suspected macular-papular rash; angioedema; non-compliance; lost to follow-up; withdrawal of consent. No safety-related trends have been identified in the ongoing Study MIV-711-201 and it is believed that MIV-711 has acceptable safety and tolerability based on blinded results in OA patients.

2.3 Study Rationale

As stated in Section 2.1, there are no pharmacological 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; this is supported by relevant animal models which demonstrate reduced structural joint degradation after treatment with MIV-711.

Whilst the first study of MIV-711 in patients, Study MIV-711-201, has the potential to establish a first indication of disease modifying efficacy for MIV-711 in OA, it is also important to consider the chronic nature of OA which often leads to life-long disease symptoms from the time of diagnosis. The life-long course of OA highlights the need to assess long-term safety for a prospective DMOAD, which is therefore the main rationale of the current extension study. While further outlining the current study MIV-711-202 in the following sections, the study population pertaining to the 12 month safety assessment in Study MIV-711-202 is henceforth described as Study Population A.

There are two further rationales for this study:

- It is known that cartilage structural changes are not expected to be apparent over a 6-month period using MRI [35] which constitutes the reason for using knee joint bone area as the main structural read-out in Study MIV-711-201. In the current study, patients will be treated for 52 (26+26) weeks (Study Population A) which will enable the secondary analysis of cartilage changes versus Baseline in Study MIV-711-201.
- Furthermore, there is no available method to predict OA progression. In Study MIV-711-201 there is a potential to identify patients treated with placebo that exhibit signs of clinical progression over the course of 26 weeks. Patients with manifest symptomatic progression of OA would constitute the most justifiable patient population to receive a DMOAD. It is believed that the proposed extension study would be the first opportunity to explore the effects of a potential DMOAD in OA

patients with verified progressive symptoms (based on symptoms reported from Study MIV-211-201). While further outlining study MIV-711-202 in the following sections, the study population pertaining to the 6 month treatment assessment in patients with progressive symptoms is henceforth described as Study Population B.

2.4 Study Design and Dosing Rationales

The present study is a 6-month open-label one-arm extension study evaluating safety and tolerability as well as the efficacy of 200 mg MIV-711 q.d. in two separate patient populations denoted as Study Populations A and B.

Study Population A will be recruited from patients treated with 200 mg MIV-711 q.d. in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the numeric rating scale (NRS) of ≤2 compared to Baseline. Patients eligible for Study Population A will be offered to roll over for 6 months' extended treatment, primarily evaluating longer term safety and tolerability. The total treatment duration of 52 weeks also allows a more suitable treatment length for the exploratory study of any structural effects of MIV-711 on joint cartilage thickness. [23, 24, 25].

There will be no continuation of the 100 mg dose from Study MIV-711-201 because from a safety and tolerability perspective, using the 200 mg dose in this extension study allows exposure to the highest dose previously tested for MIV-711. MIV-711 has also shown a higher reduction in CTX-II excretion at 200 mg compared with 100 mg q.d. Based on the established link 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 Section 2.1), it is judged that the 200 mg dose should be studied in this extension study since it has the highest potential to contribute to a disease modifying effect in OA. Extending the 200 mg dose in those patients that did not significantly deteriorate clinically in their OA on that dose during the first 26 weeks, allows a balanced assessment of the 52-week safety and tolerability of MIV-711 while at the same time maximizing the opportunity of measuring structural change on joint cartilage thickness versus Baseline. Joint cartilage thickness is believed to require an observational period of at least 12 months as described in the literature.[23, 24, 25]

A further rationale of this study is to explore the treatment effect in a group of OA patients that have confirmed symptom progression over the last 6 months (Study Population B). Study Population B will be recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus Baseline. Patients eligible for Study Population B will be offered 200 mg MIV-711 q.d. for the next 26 weeks. In addition to offering the treatment to appropriate patients, this also enables the assessment of the effects of MIV-711 based on MRI imaging, symptoms and biomarkers in patients with progressing symptoms and, as such, has the potential to provide valuable information for future patient selection in OA trials. Similar to Study MIV-711-201, the joint structural endpoint of choice over 6 months treatment constitutes MRI joint bone surface measurement (see Section 7.2).[23] All analyses, with the exception of safety and tolerability, will be conducted as exploratory with regards to Study Population B.

All patients in Study MIV-711-201 at the participating sites included in Study MIV-711-202 will be given the opportunity to participate. Patients, investigators and site staff will not be made aware of the preceding treatment allocation in Study MIV-711-201 and treatment will remain blinded until database lock of study MIV-711-201. The actual roll-over of individual patients to Study MIV-711-202 is based on the criteria for Study Populations A and B detailed above and is executed by a central person independent from the study with access to the randomisation list and eCRF for Study MIV-711-201. The patients will be considered for roll-over one by one as they complete the last treatment visit in Study MIV-711-201 and upon blinded approval of the investigator as well as provision of informed consent. Based on the

selection criteria for Study Population A and B described earlier in this section, it is anticipated that 50-80 patients will be eligible for participation. Patients will be recruited from up to 5 centres in up to 5 countries for this study. Recruitment may be terminated if considered appropriate or necessary by the sponsor.

The analysis of data from the proposed study will not be based on a formal statistical analysis since the primary endpoint constitutes safety and tolerability. All efficacy parameters measured in Study MIV-711-201 will also be measured in the proposed study. However, the important difference is that any comparisons will be made from baselines within but not between Study Population A and B. In contrast, in Study MIV-711-201, comparisons will be made between treatment groups with a formally powered analysis regarding the primary endpoint.

2.5 Risk-Benefit Assessment

The presently proposed Phase II study (MIV-711-202) is the third clinical study with MIV-711 and as such it has the potential to determine the 12 month safety of MIV-711 in treating painful, radiographic knee OA, as well as the effect over 6 months in patients with progressing symptomatology.

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 x 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 the no observed adverse effect level (NOAEL) was 15 µM x 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 q.d. for 7 days have been explored in healthy volunteers. In addition, the 100 mg dose was administered q.d. 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 q.d. in man, which constitutes the highest dose in Study MIV-711-201 as well as the only dose administered in Study MIV-711-202 resulted in a 2.4 µM x h average AUC_{0-24} which corresponds to an expected 6 times margin to the NOAEL level in the cynomolgus monkey.

MIV-711 has consistently shown biomarker effects in the Phase I study that correlates strongly with efficacy on joint structure in the pre-clinical models. The doses of MIV-711 used in Study MIV-711-201 were 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 2.1). There is further potential symptom and structure improvement benefit for patients in Study Population A in the present study as the treatment length is extended to a total of 52 (26+26) weeks on 200 mg q.d. MIV-711. This potentially allows measurable changes in cartilage to occur. Furthermore, patients in Study Population B are selected based on clinically significant symptom progression and may therefore benefit more from a potential DMOAD compared to stable patients. The potential for benefit together with the hitherto favourable safety and toxicology profile converge into a favourable Benefit/Risk assessment for the present study.

No safety-related trends have been identified in the ongoing Study MIV-711-201 and it is believed that MIV-711 has acceptable safety and tolerability in OA patients based on the blinded results so far. By the start of enrolment into the present study, at least one Data Monitoring and Ethics Committee (DMEC) meeting reviewing the safety data of

Study MIV-711-201 will have been finalized. For the present study, the DMEC will reconvene to review the unblinded safety and tolerability data after the first 25 patients complete Visit 4 and Visit 5.

With regard to previous clinical experience (see IB for further information), there are at 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 present study.

On the basis of the pre-clinical and clinical data on MIV-711 to date and the favourable Benefit/Risk balance, it is considered appropriate to proceed with the Phase II extension study which is proposed in the present protocol.

3 STUDY OBJECTIVES

3.1 Primary Objective Study Population A*

To assess the safety and tolerability of 200 mg MIV-711 q.d. over 52 (26+26) weeks in patients with symptomatic and radiographic knee osteoarthritis.

* Study Population A will be recruited from patients treated with 200 mg MIV-711 q.d. in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in NRS of ≤2 compared to Baseline.

3.2 Secondary Objectives Study Population A

To assess, in patients with symptomatic and radiographic knee OA, over 52 (26+26) weeks:

- The effect of MIV-711 on MRI cartilage thickness loss
- The effect of MIV-711 on MRI bone marrow lesion volume
- The effect of MIV-711 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- To assess the effect of MIV-711 on MRI knee joint bone area.

Note: all MRI assessments refer to the target knee unless stated otherwise.

Target knee is 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. The target knee in Study MIV-711-202 must be the same as in Study MIV-711-201.

3.3 Secondary Objective Study Population B*

To assess the effect of 200 mg MIV-711 q.d. on safety and tolerability over 26 weeks in patients with symptomatic and radiographic knee osteoarthritis.

* Study Population B will be recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus Baseline.

3.4 Exploratory Objectives Study Population A

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

- 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 patient reported e-diary daily recall knee joint pain
- The effect of MIV-711 on patient reported e-diary daily recall analgesics use
- 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 (PINP), bone specific alkaline phosphatase (BSAP), N-terminal telopeptide of collagen type I (NTX-I), CTX-I, αCTX-I, CTX-II and tartrate-resistant acid phosphatases (TRAP5b).
- Baseline and steady state treatment 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 proteomics, genomics, metabolomics and lipidomics analyses.

- The effect of MIV-711 on a compound index of MRI bone area and cartilage thickness
- The pharmacokinetics of MIV-711 and the relationship to patient factors and concomitant medications

3.5 Exploratory Objectives Study Population B

All of the above denoted secondary and exploratory parameters described in Section 3.2 and Section 3.4 for Study Population A, are considered as exploratory objectives in Study Population B and will be evaluated over 26 weeks.

4 OVERALL DESIGN AND PLAN OF THE STUDY

This is a multicentre, open-label, one-arm Phase II extension study to evaluate the safety and tolerability of MIV-711 in patients with knee joint 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.

All patients in Study MIV-711-201 (Eudract No. 2015-003230-26) at the participating sites included in Study MIV-711-202 will be given the opportunity to participate provided that they meet the eligibility criteria. The transition from Study MIV-711-201 to MIV-711-202 is shown in Figure 1.

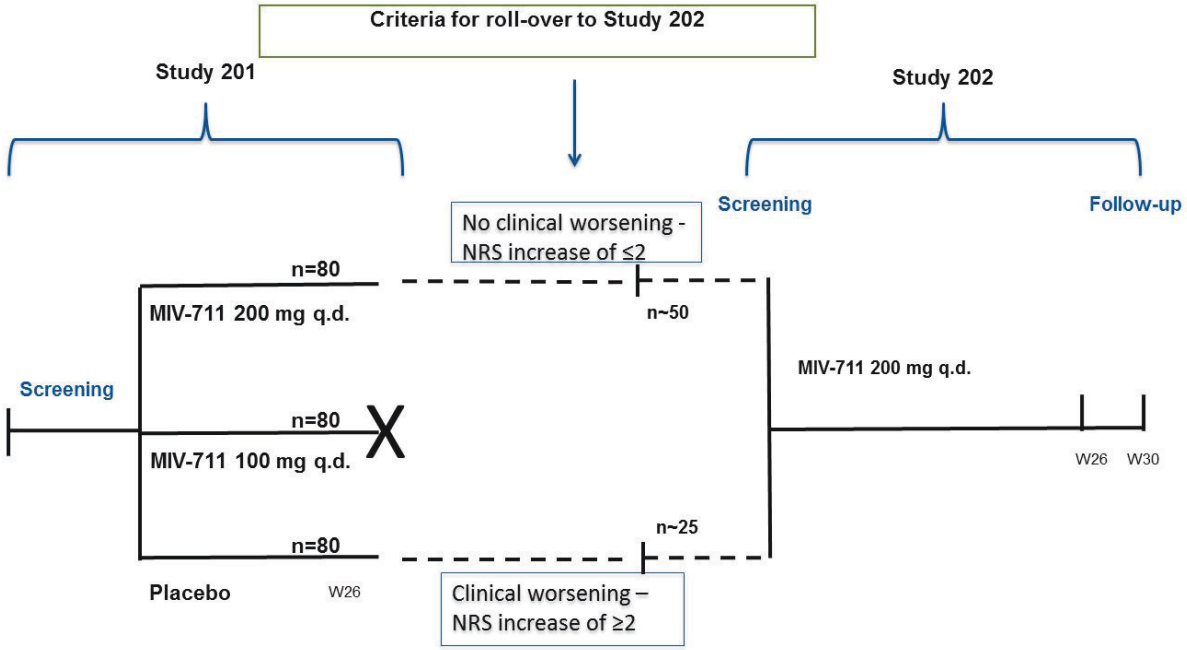

Figure 1: Transition from Study MIV-711-201 to Study MIV-711-202

To ensure the patients will have sufficient time to consider their participation in the study the informed consent form will be given to the patients prior to Visit 8 in Study MIV-711-201. Visit 8 of Study MIV-711-201 will ideally be conducted on the same day as Visit 1 of the present study. If these visits are conducted on the same day the results of the following assessments will be recorded in the electronic Case Report Form (eCRF) for both studies; urine and blood sampling for safety, vital signs, physical examination and ECG. See Section 8.1.1 for a full list of assessments required at Visit 1.

A central person, independent from the study, with access to the randomisation list and the eCRF for Study MIV-711-201 study will confirm Inclusion Criterion 1. The confirmation will be communicated to the site staff and the study team via fax/email without revealing the treatment in MIV-711-201 or the change in NRS score.

All enrolled patients will receive 200 mg q.d. oral dose of MIV-711 for 26 weeks in addition to their current medication. MIV-711 200 mg will be provided as identical capsules to those used in Study MIV-711-201.

The patients will take the last dose of IMP in Study MIV-201-711 at Visit 8 and dosing in the present study will be started at Visit 2 after a screening period of 10±5 days. Patients who are

not eligible to participate in the present study will return for the safety follow up visit (Visit 9) in Study MIV-711-201.

Patients will be permitted to remain on their current analgesic regimen with any changes in concomitant medications reported and recorded at study visits as well as in a patient reported daily e-diary for two 2-week periods prior to Visit 4 and Visit 5.

The study consists of a Screening period of approximately 2 weeks (Visit 1), eligibility at Visit 2, an open-label treatment period of 26 weeks from Visit 2 through Visit 5, and a follow-up period of 4 weeks (Visit 6) after the last dose of study treatment is administered. Telephone calls will be made 5-9 days after all dosing visits for safety and tolerability. There will be additional phone calls at Week 10 and Week 20 for safety and tolerability.

A DMEC will meet to review the unblinded safety and tolerability data after the first 25 patients complete Visit 4 and Visit 5.

The study design is summarised in Figure 2.

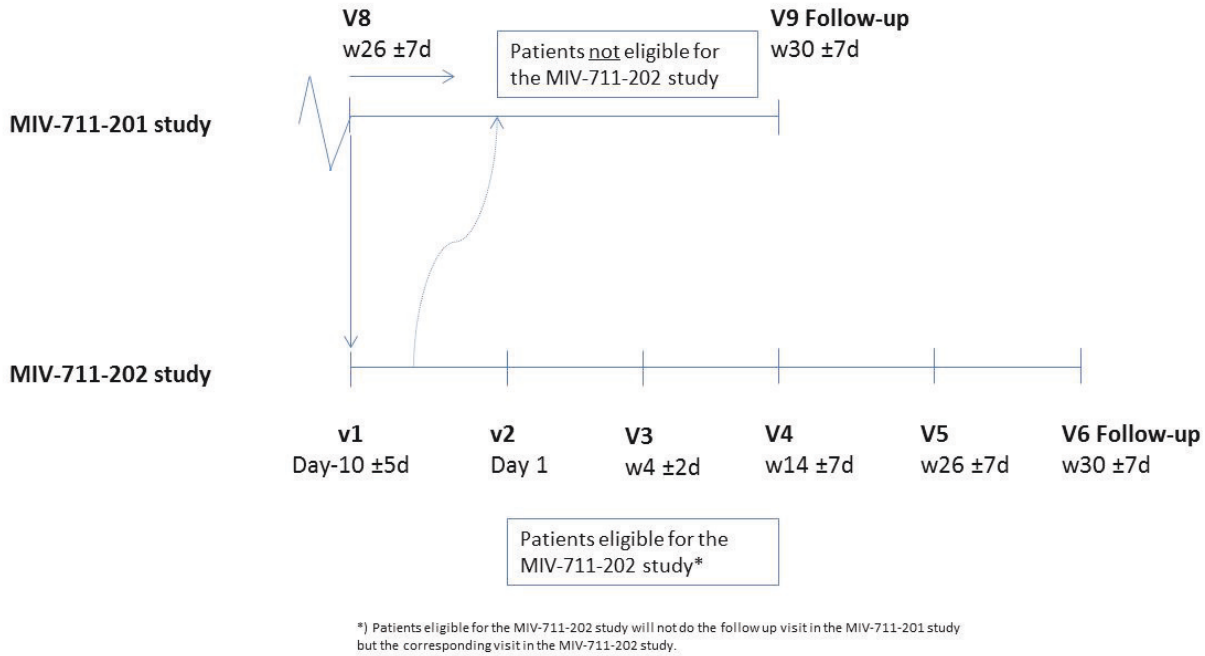

Figure 2: Study Design

5 STUDY POPULATION

The study population will consist of patients with symptomatic and radiographic knee joint OA who have participated in Study MIV-711-201. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

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

1. Previously enrolled in Study MIV-711-201 including completion of Visit 8 either by

   - Receiving MIV-711 200 mg and had non-significant clinical worsening on the primary endpoint as defined by NRS increase of ≤2

   OR by

   - Receiving placebo and had a clinically significant worsening on the primary endpoint as defined by NRS increase of ≥2

   The NRS result will be derived using the primary endpoint from Study MIV-711-201: NRS average knee pain in the target knee with 7 days recall: increase from Baseline (Visit 2 of Study MIV-711-201) to Visit 8 of Study MIV-711-201.

2. 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 amenorrhoeic for 12 months without an alternative medical cause and with a Screening follicle stimulating hormone test indicating post-menopausal state.

3. 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).

4. The patient's usual analgesic regimen (in case of use) should remain the same as for Visit 8 in Study MIV-711-201 (i.e., Visit 1 in Study MIV-711-202).

   NOTE: 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 during his/her participation in the study, then this will be allowed and should be properly documented in the patient file and the CRF.

5. Needs to be able to communicate well with the investigators and staff.

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

5.2 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. Ongoing or a history of atrial fibrillation.
4. Currently receiving medication that affects cartilage or bone metabolism (other than study drug; hormone replacement therapy taken for more than 6 months is allowed).
5. Current or recurrent disease that could affect the action, absorption or disposition of MIV-711, or could affect clinical assessments or clinical laboratory assessments.
6. 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.
7. Any medical condition, AE, clinical or laboratory finding from Study MIV-711-201 that, in the opinion of the Investigator, would preclude inclusion in the present clinical study.
8. Known or suspected intolerance or hypersensitivity to the investigational medicinal product, closely related compounds, or any of the stated ingredients.
9. History of alcohol or other substance abuse within the last year.
10. Use of an investigational product other than MIV-711 during participation in Study MIV-711-201 and /or active enrolment in another drug or vaccine clinical study.
11. Significant target knee injury or surgery during participation in Study MIV-711-201.
12. 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.
13. 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 venepuncture or lack of adequate venous access for required blood sampling during the study period).
14. Use of intra-articular hyaluronic acid in the target knee during participation in Study MIV-711-201.
15. Use of intra-articular, intra-muscular or oral corticosteroids during participation in Study MIV-711-201.
16. Commencement of non-pharmacological OA interventions during participation in Study MIV-711-201.
17. 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.

18. Lack of MRI of the knee from Visit 8 in Study MIV-711-201 due to special circumstances, such as claustrophobia or difficulties to fit the knee coil.
19. Patients with contra-indication to MRI of the knee.

5.3 Patient Withdrawal and Replacement

In accordance with the Declaration of Helsinki, GCP, and International Conference on Harmonisation (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 AEs and will be asked to return for a follow-up visit (similar to Visit 6) within 4 weeks following the withdrawal. An MRI scan should be completed if withdrawal is after Visit 4.

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 clinical research associate (CRA) should be informed as soon as possible.

If the patient has not yet received any IMP in the current protocol 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 of the reasons listed below:

- The occurrence of pregnancy in a patient.
- Use of a non-permitted concomitant drug, as defined in Section 6.6.4 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 end of treatment (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 (alanine aminotransferase [ALT] and/or aspartate aminotransferase [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 ms 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 medication will be asked to still complete their follow-up visit (Visit 6) 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).

5.4 Planned Sample Size and Number of Study Centres

All patients in Study MIV-711-201 at the participating sites in Study MIV-711-202 will be given the opportunity to participate provided that they meet the eligibility criteria.

It is expected that approximately 50-80 patients based on the normal progression rate of OA symptoms, as well as the study selection criteria, will be eligible for participation. However due to unpredictable factors such as perceived benefits or burdens for the patients participating in the study the estimated total number of patients may deviate from the range above.

The patients will be recruited from up to 5 centres in up to 5 countries for this study. Recruitment could be terminated if considered appropriate.

5.5 Patient Identification

5.5.1 Patient Identification

The Principal Investigator or qualified designee 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 patient number. Screened patients who drop out of the study before the first administration of IMP in Study MIV-711-202 will retain their patient number. The MIV-711-202 study will be an open-label study and distribution of IMP will proceed through the use of an Interactive Response Technology (IRT) System [Interactive Web Response System (IWRS)].

5.5.2 Investigational Drug Administration Scheme

From the patients with knee joint OA participating in Study MIV-711-201, those who meet the eligibility criteria for the extension study and who provide written informed consent will be included in the extension study. In Study MIV-711-202, all patients will receive 200 mg q.d. oral dose of MIV-711 for 26 weeks in addition to their current medication. MIV-711 200 mg will be provided as identical capsules to those used in Study MIV-711-201.

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

5.5.3 Allocation of Patients to Treatment

Allocation of patients to treatment will occur at Visit 2 (Enrolment) after the patient has signed the informed consent form and the Investigator has confirmed the patient's eligibility based on screening procedures performed. All patients will receive a unique patient number. The patient 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.

5.5.4 Procedures for Handling of Incorrectly Included Patients

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 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 5.3).

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.

6 STUDY DRUG

6.1 Investigational Drug

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

MIV-711 is formulated in hard gelatin capsules (size 0) at the strength of 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.

6.2 Administration

Patients will receive q.d. 200 mg oral dose of MIV-711 for 26 weeks in addition to their current medication.

The IMP should be taken q.d. 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 in Study MIV-711-202 is administered at the site during Visit 2 (Enrolment). All patients must stay at the site 2 hours after administration of the first dose.

IMP should be dispensed during the Visits 2 and 4 and returned by the patients for drug accountability at Visit 4 and Visit 5.

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

6.3 Packaging, Labelling and Storage

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

The packaging and labelling of the patient packages will be performed in accordance with Good Manufacturing Practice (GMP) and national requirements. The labelling 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.

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

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

The investigator must immediately inform the CRA in case of any temperature excursions.

Shorter (≤ 24 hours) periods of storage outside the 15°C to 25°C range is accepted if maximum temperature does not exceed 40°C.

6.4 Drug Accountability

The Investigator is responsible for maintaining accurate IMP accountability records throughout the study. The 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 Section 6.3. 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.

6.5 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 enrolment in the study. 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).

6.6 Other Medications

6.6.1 Rescue Medication

Where possible, patients will be asked to continue with the same analgesic or anti-inflammatory medication 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.

6.6.2 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 q.d. 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 elimination 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 documents and eCRF. 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 at the time of Visit 1 will be documented as prior medication. Medication taken after the first dose of IMP in the current (MIV-711-202) study will be documented as concomitant medication. All patients will be asked about concomitant medication use and any changes to use of concomitant medications at all study visits. Patients will be permitted to reinstate prohibited concomitant medications on completion of their follow up study visit.

6.6.3 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 as at Visit 8 in Study MIV-711-201. 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.

6.6.4 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 inhibiting antibodies and calcitonin. Apart from combinations with mild opioids as specified in Section 6.6.3, all opioids are prohibited unless for occasional rescue medication purposes. In case of uncertainty regarding prohibited medications please contact the medical monitor.

6.6.5 Chondroitin and Glucosamine

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

6.7 RESTRICTIONS

The present study, MIV-711-202 is an extension to the main study MIV-711-201. The main study was started with limited available data on phototoxicity for the study drug MIV-711 which necessitated protective sunlight measures for participating patients. Further evaluation of MIV-711 in laboratory tests have since been undertaken which concluded that there is no phototoxicity risk for patients taking MIV-711. However, since the present study is an extension, it is advised that patients follow similar sunlight protective measures in order to maintain consistency in study conditions for patients in the two studies. Such sun and ultra violet (UV)-light protective measures include 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.

7 ENDPOINT AND METHODS OF ASSESSMENT

7.1 Primary Endpoint (Study Population A)

The primary objective is to study the safety and tolerability of MIV-711 in OA patients who have received treatment for up to 52 (26+26) weeks.

Safety endpoints:

- Incidence and severity of AEs
- Incidence and severity of clinical laboratory abnormalities
- Physical examination findings by patient
- Incidence and severity of ECG abnormalities
- Mean change from Baseline (Visit 2 of Study MIV-711-201) in vital signs (blood pressure, heart rate, temperature) and oxygen saturation
- Categorical summary of observed vital signs and vital sign changes compared to Baseline (Visit 2 of Study MIV-711-201), by patient

7.2 Secondary Endpoints (Study Population A)

Bone parameters will be measured from MRIs of the bone area taken at Visit 2 (Enrolment) and Visit 8 of Study MIV-711-201 as well as the MRI of the bone area taken at Visit 5 in Study MIV-711-202.

MRIs will be analysed semi-quantitatively by a central experienced musculoskeletal radiologist using the MOAKS [36] and quantitatively using statistical shape modelling (SSM, Imorphics Ltd) for the features below. [23, 37, 38]

MOAKS scoring will be used to assess the following features:

- Bone marrow lesions (BMLs) and cysts: 15 sub-regions graded for BML (including ill-defined lesions and cysts) size in regard to the total volume of the sub-region occupied by BML(s). Grade 0=none, grade 1<33% of sub-regional volume, grade 2=33–66% of sub-regional volume and grade 3>66% of sub-regional 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 sub-region 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.

Bone shape modelling of MRI 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 [39]
- 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 patella
- Bone 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.

7.3 Secondary Endpoints (Study Population B)

These are the same as the primary endpoints for Study Population A (see Section 7.1).

7.4 Exploratory Endpoints

7.4.1 Exploratory Endpoints (Study Population A)

Patient-reported outcomes (PROs)

At Visit 4 and 5 the following PROs 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 [40] - a 24-item OA-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in OA of the knee. The response to each question is 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 [41, 42] 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) [42] - 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 [43] 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) [44] (Visit 5 only) - 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 [45]. 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.[46]

- In an e-diary format, a patient knee pain diary (NRS) and analgesia questionnaire will be completed daily during two 2-week periods prior to Visit 4 and Visit 5. Baseline (Visit 2 of Study MIV-711-201) 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

Biomarkers, imaging and pharmacokinetics:

- Serum and urinary biomarkers (CTX-I, PINP, BSAP and TRAP5b in serum and NTX-I, CTX-I, αCTX-I, and CTX-II in urine).
- Compound index of MRI bone area and cartilage volume
- Pharmacokinetics: MIV-711 PK parameters and their relationship to covariates such as age, weight, gender, liver function and concomitant medications.

7.4.1.1 Biomarkers and biobanking

Blood and urine samples will be taken at Visits 2, 4, 5 and 6, for analysis of exploratory bone and cartilage markers of relevance for OA disease, such as CTX-I, PINP, BSAP and TRAP5b in serum and NTX-I, CTX-I, αCTX-I and CTX-II in urine.

A blood and urine sample from Visit 5 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.

7.4.1.2 Imaging

Change from Visit 8 in Study MIV-711-201 to Visit 5 in the current study in a calculated compound index of MRI bone area (key secondary endpoint) and cartilage thickness.

7.4.1.3 Pharmacokinetics

The pharmacokinetics and potential metabolites of MIV-711 and their relationship to patient factors and concomitant medications will be analysed following the sampling procedures as described in Section 7.10.

7.4.2 Exploratory Endpoints (Study Population B)

All secondary and exploratory endpoints described in Section 7.2 and Section 7.4.1, respectively, for Study Population A will be assessed as exploratory endpoints for Study Population B and will be evaluated over 26 weeks.

7.5 Physical Examination

A standard complete physical examination will be performed at Visit 1 (Screening), Visit 2 (Enrolment), Visit 3, Visit 4 and Visit 5. 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, lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremities exam for the presence of peripheral oedema, abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

A standard clinical examination of both knees will be undertaken at all visits. Any clinically significant changes from Visit 2 (Enrolment) should be recorded as AEs.

7.6 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.

Weight will be measured at Visit 1 (Screening).

7.7 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 (Enrolment) pre-dosing and after 30 minutes, 1 hour and 2 hours post-dosing (± 10 minutes).

On dosing days, ECG should be performed 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.

7.8 Imaging Assessments

At Visit 5 MRI acquisition will be performed on the bone area 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 as used during Visit 2 and Visit 8 in Study MIV-711-201.

Based on experience from Study MIV-711-201 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. Each set of images will be quality controlled to allow for a repeat MRI to be captured if required. 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 image quality issues the central reader may request the

phantom scans. If a site has an upgrade (hardware/software) then a phantom scan will be requested before and after upgrade to confirm the protocol has not changed.

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.

7.9 Self-report Parameters

Patient-reported outcomes will be recorded using questionnaires at Visit 4 and at Visit 5, as follows:

Pain, function and disease activity

- 11-point NRS scales for:
  - Average overall knee pain severity in the target knee over the past 1 week
  - Average overall knee pain severity in the contralateral knee over the past 1 week
  - 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 two 2-week periods prior to Visit 4 and prior to Visit 5.

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

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. This will be performed at Visit 5 only.

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 AEs since the last visit, or the outcome of any AEs 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 4 and Visit 5 and drug accountability will be conducted. The Brief Medication Questionnaire self-reported measure [47] for the use of concomitant medication will be included at Visit 4 and Visit 5.

7.10 Pharmacokinetic Sampling

Three blood samples will be collected at Visit 5 to measure plasma concentrations of MIV-711 and potential metabolites. On this visit, 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 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 1500 g for 10 minutes at approximately 4°C.

For each sample, the separated plasma will be equally split into 2 aliquots and transferred into 2 suitably labelled polypropylene tubes, and stored within 2 hours of collection at at least -70°C until shipped on dry-ice. The 2 aliquots should be shipped in two separate shipments to the Bioanalytical Laboratory for further shipment and analysis of MIV-711 and for potential metabolite analysis. 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 analysing 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.

7.11 Biomarker Sampling

Blood and urine samples will be taken at Visits 2, 4, 5 and 6 for analysis of exploratory bone and cartilage biomarkers of relevance for OA disease, such as CTX-I, PINP, BSAP and TRAP5b in serum and NTX-I, CTX-I, αCTX-I and CTX-II 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 the visit.

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 labelled 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 labelled 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.

Aliquot 1 and 2 of each blood and urine sample should be shipped together to the Central Laboratory. The third aliquot should remain at the site and be shipped separately.

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

7.12 Optional Pharmacogenomics Sampling

Blood and urine samples will be collected at Visit 5 under voluntary ICF 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.

The 2 aliquots of each blood and urine sample should be shipped in two separate shipments to the Central Laboratory.

7.13 Adverse Events

7.13.1 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 unfavourable 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.

7.13.2 Assessment of Adverse Events

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

7.13.2.1 Seriousness

An 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.

7.13.2.2 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.

7.13.2.3 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

7.13.2.4 Adverse Events of Special Interest

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

7.13.2.5 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 6) 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.

7.13.2.6 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 6) 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 a valid report:

- An identifiable reporter (i.e., name, address of Investigator)
- An identifiable patient (i.e., patient 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 centre 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

7.13.2.7 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 stabilized 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.

7.13.2.8 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 Regulatory Authorities and Independent Ethics Committees (IECs) will be notified within 7 calendar days after 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 Regulatory Authorities and IECs will be notified within 15 calendar days after PAREXEL 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.

7.13.2.9 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 by providing the completed Pregnancy Reporting and Outcome Form within 24 hours of awareness and followed until outcome (completion/termination) of the pregnancy.

7.13.2.10 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 Reporting and Outcome 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 7.13.2.6.

7.13.2.11 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 7.13.2.6.

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 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.

8 STUDY CONDUCT

8.1 Study Schedule

Patients with symptomatic knee OA participating in Study MIV-711-201 will be invited to participate in the present study.

Visit 1 of the present study coincides with Visit 8 of Study MIV-711-201. To ensure the patients will have sufficient time to consider their participation in the study, the informed consent form will be given to the patients prior to Visit 8 in Study MIV-711-201. During Visit 1 of the present study the patient information will be discussed. Any questions from the patient will be answered. The Screening Phase will last for a maximum of 10±5 days, during which patients will be checked for eligibility by the investigator. The patient's eligibility will be determined by the laboratory results obtained during the Screening visit (Visit 1). The study will include 26 weeks of treatment, with patients followed for 30 weeks as per Study Schedule (Table 2).

8.1.1 Screening Visit (Visit 1, Day -10 ± 5 days)

The activities below are those performed 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. The patient will have been provided with the consent form to read prior to Visit 8 in Study MIV-711-201.
- Assessing inclusion and exclusion criteria
- Obtaining demographic data (including age, gender and race)
- Obtaining medical and surgical history
- Performing complete physical examination (assessed at Visit 8 in MIV-711-201, must only be re-assessed if Visit 8 does not occur on the same day as Visit 1 in the present study)
- Performing vital signs assessments including weight and oxygen saturation (assessed at Visit 8 in MIV-711-201, must only be re-assessed if Visit 8 will not occur on the same day as Visit 1 in the present study)
- Performing 12-lead electrocardiogram assessment (assessed at Visit 8 in MIV-711-201, must only be re-assessed if Visit 8 will not occur on the same day as Visit 1 in the present study)
- Sampling for urinalysis (assessed at Visit 8 in MIV-711-201, must only be re-assessed if Visit 8 will not occur on the same day as Visit 1 in the present study)
- Sampling for urine drug screen
- Sampling for blood clinical chemistry and haematology testing (assessed at Visit 8 in MIV-711-201, must only be re-assessed if Visit 8 will not occur on the same day as Visit 1 in the present study)
- Sampling for blood post-menopausal assessments (only post-menopausal or sterile women will be enrolled)
- Dispensing new Patient Emergency Card
- Monitoring for AEs, SAEs
- Performing registration in the Interactive Web Response System (IWRS)

8.1.2 Enrolment (Visit 2, Day 1)

The activities below are those performed at the enrolment visit which will be documented in eCRF:

- Confirming inclusion and exclusion criteria
- Monitoring for AEs, SAEs and concomitant medication
- Performing complete physical examination
- Performing vital signs assessments
- Performing 12-lead serial ECGs at Visit 2 (Enrolment) pre-dosing and after 30 minutes, 1 hour and 2 hours post-dosing (± 10 minutes)
- Sampling for blood and urine biomarker testing
- Sampling for blood clinical chemistry, haematology and urine testing
- Dispensing the first IMP at the site. Patient must stay at the clinic for 2 hours after taking the IMP.
- Dispense e-diary. Re-training of patients if required.
- Obtaining optional ICF for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics.
- Phone call to assess safety and tolerability (completed 5-9 days after the visit)

8.1.3 Safety Visit (Visit 3 [Week 4 ± 2 days])

The activities below are those performed at the safety visit which will be documented in eCRF:

- Monitoring for AEs, SAEs and concomitant medication
- Performing vital signs assessments
- Performing physical examination
- Performing 12-lead electrocardiogram assessment 30 minutes post-dose
- Sampling for urinalysis
- Sampling for blood clinical chemistry and haematology testing
- Phone call to assess safety and tolerability (completed 5-9 days after the visit)

8.1.4 Safety and Treatment Visit (Visit 4 [Week 14 ± 7 days], and Visit 5 [Week 26 ± 7 days])

The activities below are those performed at the safety and treatment visits which will be documented in eCRF:

- Monitoring AEs, SAEs and concomitant medication
- Performing vital signs assessments
- Performing complete physical examination
- Performing 12-lead electrocardiogram assessment 30 minutes post-dose (± 10 minutes)
- Sampling for urinalysis
- Sampling for blood and urine biomarker testing
- Sampling for blood clinical chemistry and haematology testing
- Sampling for blood PK assessment (at Visit 5 only)
- Obtaining optional blood sample for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine sample for proteomics and metabolomics (at Visit 5 only)
- Performing knee MRI (at Visit 5 only) ±5 days

- Completion of NRS, WOMAC, ICOAP, Global Improvement Questionnaire and Brief Medication Questionnaire
- Completion of Quality of Life questionnaire: EuroQoL EQ-5D-5L (at Visit 5 only)
- Dispense IMP at the site (the capsule should be taken from the bottle currently in use by the patient) (Visit 4 only)
- Drug accountability
- Review e-diary completion which has been done for a two-week period prior to the visits
- Phone call to assess safety and tolerability (completed 5-9 days after the visits)
- Return of e-diary (at Visit 5 only)

8.1.5 Additional Telephone Calls to Assess Safety and Tolerability

Additional telephone calls to assess safety and tolerability will be performed at Week 10 and Week 20.

8.1.6 Safety Follow-up Visit (Visit 6, Week 30 ± 7 days)

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

- Monitoring AEs, SAEs and concomitant medication
- Performing vital signs assessments
- Performing 12-lead electrocardiogram assessment
- Sampling for blood and urine biomarker testing
- Sampling for blood clinical chemistry, haematology and urine testing

The end of the study is defined as the last Visit 6 (Week 30) of the last patient.

Table 1: Clinical Laboratory Testing

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 amenorrheic for 12 months without an alternative medical cause and with a Screening FSH indicating post-menopausal state.
Fasting samples are required at all study visits as fasting glucose is required as part of the chemistry samples.
Haematology: WBC and differential, % and absolute for: neutrophils, lymphocytes, monocytes, eosinophils, basophils; haemoglobin, haematocrit, 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
Urinalysis: with microscopic: specific gravity, pH, protein, glucose, ketones, nitrites, blood and leukocyte esterase
Urine Drug Screen: Amphetamine, Benzodiazepines, THC, Cocaine, Oxycodone and Opiate
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**
Weeks	**-2**	**1**	**4 ±2 days**	**14 ±7 days**	**26 ± 7 days**	**30 ± 7 days**
Day	**-10 ± 5 days**	**Day 1**	**28 ±2 days**	**98 ±7 days**	**182 ± 7 days**	**210 ± 7 days**
Visit Description	**Screening[A]**	**Enrolment**	**Safety**	**Safety and Treatment**		**Safety follow-up**
Signed informed consent	X	X[B]				
Inclusion/exclusion criteria	X	X				
Demographics	X					
Weight	X					
Medical & Surgical history	X					
Physical examination	X[C]	X	X	X	X	
Vital signs, including body temperature	X[C]	X	X	X	X	X
12-Lead ECG[D]	X[C]	X[E]	X	X	X	X
Clinical chemistry/Haematology	X[C]	X	X	X	X	X
Urinalysis[F]	X[C]	X	X	X	X	X
Urine drug screen	X					
Post-menopausal assessment (females only)	X					
e-diary dispensing and training		X				
e-diary for pain and analgesic[G]				X	X	
Patient Emergency Card Dispensing	X					
MRI of the bone area					X[H]	

Study Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Weeks	**-2**	**1**	**4 ±2 days**	**14 ±7 days**	**26 ± 7 days**	**30 ± 7 days**
Day	**-10 ± 5 days**	**Day 1**	**28 ±2 days**	**98 ±7 days**	**182 ± 7 days**	**210 ± 7 days**
Visit Description	**Screening[A]**	**Enrolment**	**Safety**	**Safety and Treatment**		**Safety follow-up**
Registration in the IWRS	X					
NRS, ICOAP, WOMAC				X	X	
Global improvement (6-point Likert scale)				X	X	
EuroQoL EQ-5D-5L					X	
Brief Medication Questionnaire				X	X	
Dispense IMP[I]		X[J]		X		
Drug accountability				X	X	
e-diary return					X	
PK sampling (blood)					X	
Biomarker samples[K]		X		X	X	X
AEs/SAEs monitoring	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X
Phone call to assess safety and tolerability[L]		X	X	X	X	
Blood sample for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine sample for proteomics and metabolomics					X[M]	

Study Visit	V1	V2	V3	V4	V5	V6
Weeks	-2	1	4 ±2 days	14 ±7 days	26 ± 7 days	30 ± 7 days
Day	-10 ± 5 days	Day 1	28 ±2 days	98 ±7 days	182 ± 7 days	210 ± 7 days
Visit Description	Screening[A]	Enrolment	Safety	Safety and Treatment		Safety follow-up

Abbreviations: AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; DNA=deoxyribose nucleic acid; EuroQoL EQ-5D-5L= 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; FSH=follicle stimulating hormone; ICF=informed consent form; ICOAP=intermittent and constant osteoarthritis pain; IMP=investigational medicinal product; IWRS= Interactive Web Response System; MRI=magnetic resonance imaging; NRS=numeric rating scale; PK=pharmacokinetic; PRO=patient-reported outcomes; RNA=ribonucleic acid; SAE=serious adverse event; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

A) The Screening visit (Visit 1) will coincide with 26-week End of Treatment visit of Study MIV-711-201 (Visit 8).
B) Optional ICF to be provided and signed at Visit 2.
C) Assessed at Visit 8 in Study MIV-711-201. Only need to be re-assessed if Visit 8 does not occur on the same day as Visit 1 in Study MIV-711-202
D) 30 minutes post-dose (± 10 minutes).
E) 12-lead serial ECGs will be recorded at Visit 2 (Enrolment) pre-dosing and after 30 minutes, 1 hour and 2 hours post-dosing (± 10 minutes).
F) If urinalysis is positive for blood, nitrites, leukocyte esterase, and/or protein, additional microscopic analysis may be performed.
G) To be completed at home during the 2 weeks leading up to the marked visit with final recording the day before.
H) ± 5 days
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 5.
J) The first dose of IMP will be dispensed to the patient at the site and the patient must stay at the clinic for 2 hours after intake of IMP. Date and time should be recorded in the eCRF. The first dose should be given to the patient after all assessments at Enrolment have been performed.
K) 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.
L) The phone call should be made 5-9 days after all dosing visits. There will be additional phone calls at Week 10 and Week 20.
M) Blood will be collected for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine will be collected for proteomics and metabolomics pre-dose at Visit 5 from patients who provide additional written consent.

8.2 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 6) as outlined in the study schedule (Table 2). In addition to the assessments described in Section 8.1.6, the following should also be completed:

- Drug accountability
- Return of eDiary
- Physical examination
- Performing knee MRI (±5 days) (if withdrawal is after Visit 4)
- Obtaining optional blood samples for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics and urine samples for proteomics and meabolomics.

8.3 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 DMEC. Any SAE 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 the first 25 patients have completed Visit 4 and 5. No formal statistical tests will be undertaken but AEs will be summarised and tabulated for each group separately. If, in the view of the DMEC, the number or severity of adverse events 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 unfavourable 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 unfavourable 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.

9 STATISTICAL METHODS

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

Before 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.

9.1 Study Patients

9.1.1 Disposition of Patients

The number and percentage of patients entering and completing each phase of the study will be presented overall. Reasons for withdrawal pre- and post-randomisation will also be summarised.

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.

9.1.2 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 data base hard lock.

9.1.3 Analysis Sets

Study Population A

Patients treated with 200 mg MIV-711 q.d. in Study MIV-711-201 whose symptoms did not clinically significantly deteriorate as defined by an NRS increase of ≤2 compared to Baseline.

Study Population B

Patients receiving placebo in Study MIV-711-201 and that had experienced a clinical worsening as defined by increased NRS versus Baseline of ≥2.

No comparisons between Study Populations A and B will be undertaken.

Major protocol violators and exclusions from the analysis sets 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 analysis set:

- Incorrect diagnosis
- Any of the prohibited interventions/injuries for the target knee
- Missing more than 7 doses of MIV-711

The panel will review these criteria using soft-locked data prior to data analysis.

The safety analysis set (SAF): all patients receiving at least one dose of either MIV-711.

The primary analysis will be based on Study Population A.

The secondary analysis will be based on Study Population B.

All safety analyses will be based upon the SAF.

Demographic and Baseline characteristics will be evaluated for the SAF.

9.2 General Consideration

Continuous data will be summarised 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).

9.2.1 Power and Sample Size Consideration

This study is not powered for any confirmatory analyses.

9.2.2 Analysis and Data Conventions:

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 haemolysed 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.

9.3 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, presented overall.

9.4 Treatment Compliance

Treatment compliance as measured in Section 6.5 will be summarised by means of descriptive statistics (n, mean, SD, median, minimum, and maximum) and/or frequency tables presented overall.

9.5 Statistical Methodology

9.5.1 Primary Endpoint (Study Population A)

The primary outcome will be to study the safety and tolerability of 200 mg MIV-711 q.d. over 52 (26+26) weeks in patients with symptomatic and radiographic knee OA.

Safety endpoints:

- Incidence and severity of AEs
- Incidence and severity of clinical laboratory abnormalities
- Physical examination findings by patient
- Incidence and severity of ECG abnormalities
- Mean change from Baseline (Visit 2 of Study MIV-711-201) in vital signs (blood pressure, heart rate, temperature) and oxygen saturation
- Categorical summary of observed vital signs and vital sign changes compared to Baseline (Visit 2 of Study MIV-711-201), by patient

Safety and tolerability will be assessed descriptively in summary tables presented over time. All data presentations addressing the primary outcome will use Study Population A.

9.5.2 Secondary Endpoints

9.5.2.1 Definition of Baseline for Secondary Endpoints

For the efficacy parameters, for Study Population A, changes from Baseline will be assessed using the Visit 2 baseline data from MIV-711-201. For Study Population B, changes from Baseline will be assessed using the Visit 2 data from Study MIV-711-202.

9.5.2.2 Study Population A

The secondary endpoints are related to efficacy:

- The effect of MIV-711 on MRI cartilage thickness loss
- The effect of MIV-711 on MRI bone marrow lesion volume
- The effect of MIV-711 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- To assess the effect of MIV-711 on MRI knee joint bone area.

Note: all MRI assessments refer to the target knee unless stated otherwise.

9.5.2.3 Study Population B

The secondary endpoint for Study Population B is the same as the primary endpoint for Study Population A (see Section 9.5.1).

9.5.2.4 Statistical Methodology for Secondary Endpoints

For Study Population B, the safety and tolerability of 200 mg MIV-711 for 26 weeks will be studied in OA patients with clinical worsening during the placebo treatment in the MIV-711-201 study. Safety and tolerability will be assessed descriptively in summary tables presented over time.

All other secondary analyses will be undertaken using Study Population A, while they will be undertaken as exploratory analyses on Study Population B.

For Study Population A all secondary outcome variables will be analysed using descriptive summary tables presenting statistics for, number of non-missing values means, medians, standard deviations, minimum and maximum values. Frequency tables (counts and

percentages) will be presented in tables where appropriate. Figures of secondary response over time will be presented as appropriate.

For all outcome variables analysed using a linear model, 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 secondary 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).

9.5.3 Exploratory Endpoints

The exploratory endpoints are detailed in Section 7.4.1 for Study Population A and Section 7.4.2 for Study Population B.

9.5.3.1 Definition of Baseline for Exploratory Endpoints

For the efficacy parameters, for Study Population A, changes from Baseline will be assessed using the Visit 2 baseline data from MIV-711-201. For Study Population B, changes from Baseline will be assessed using the Visit 8 data from Study MIV-711-201 which is expected to occur on the same calendar day as Visit 1 in Study MIV-711-202. For the biomarkers in Study Population B, the baseline will be Visit 2 in the present study (MIV-711-202).

9.5.3.2 Statistical Methodology for Exploratory Endpoints

The exploratory analysis of patient reported outcomes, bone and cartilage biomarkers, MRI imaging and PK assessments will 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 potential metabolites of MIV-711 will be an additional exploratory endpoint and will be reported as outlined above. In the analysis of biomarkers that are sampled at multiple visits, all sampled time points will be considered for change from Baseline in the respective cases. In applicable cases, PK and biomarker data may be analysed using area under the curve calculations.

9.5.4 Safety

The primary purpose and endpoint of the present study is safety and tolerability as described above. 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 scheduled assessment for the SAF. Summary statistics (number of observations, mean, SD, median, minimum and maximum values) will be presented for continuous variables, and number and percentages (n, %) will be presented for categorical variables. Where applicable, changes from Baseline will also be summarised over time.

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 and preferred term in the SAF. Treatment-emergent adverse events will be further summarised 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.

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

The number of patients taking rescue medication (see definition in Section 6.6.1), the amount of rescue medication taken and the reason for use will be tabulated and summarised descriptively.

9.6 Interim Analyses

No interim analysis will be conducted for any efficacy endpoint.

An unblinded interim safety analysis may be conducted after the first 25 patients have completed Visit 4 and Visit 5. No formal statistical tests will be undertaken. Adverse events will be summarised descriptively and tabulated for all patients by treatment group (see Section 9.5.4). 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 interim analysis of non-safety data.

10 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.

10.1 Data Quality Assurance

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 for this study must be consistent with the patients' source documentation (i.e., medical records).

10.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study centre using eCRFs. Data from external sources (such as laboratory data and eDiary 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. 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.

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.

10.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRF 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.

10.2.1 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 rights 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 entered into the eCRF.

10.3 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 monitor 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 audits 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.

10.4 Data Processing

All data will be entered by site personnel into the eCRF (as detailed in Section 10.2.1).

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.

10.5 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 the first 25 patients have completed Visit 4 and Visit 5.

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 will include three members: an independent chair having specialist osteoarthritis expertise and experience of studies in this area, an independent statistician and a second physician. 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.

10.6 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.

10.7 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.

10.8 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.

10.9 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.

10.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/Regulatory 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/Regulatory 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.

10.11 Duration of the Study

The study will be conducted from September 2016 to August 2017.

10.12 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.

10.13 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 Institutional Review Boards/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.

10.14 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.

10.15 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.

11 REFERENCE LIST

1 World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

2 Murray, C. J., et al. (2012). "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010." Lancet 380(9859): 2197-2223.

3 Vos, T., et al. (2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010." Lancet 380(9859): 2163-2196.

4 Peat, G., et al. (2001). "Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care." Ann Rheum Dis 60(2): 91-97.

5 Conaghan, P. G., et al. (2008). "Care and management of osteoarthritis in adults: summary of NICE guidance." BMJ 336(7642): 502-503.

6 Hochberg, M. C., et al. (2012). "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee." Arthritis care & research 64(4): 455-474.

7 Zhang, W., et al. (2010). "OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009." Osteoarthritis Cartilage 18(4): 476-499.

8 Pendleton, A., et al. (2000). "EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT)." Ann Rheum Dis 59(12): 936-944.

9 Conaghan, P. G., et al. (2012). "The personal impact of osteoarthritis on individuals and how they use therapies: the arthritis care OA Nation 2012 Survey." Ann Rheum Dis 71(Suppl3): 584.

10 Conaghan, P. G., et al. (2014). "Impact and therapy of osteoarthritis: the Arthritis Care OA Nation 2012 survey." Clinical Rheumatology.

11 Herrero-Beaumont, G. and J. A. Roman-Blas (2013). "Osteoarthritis: Osteoporotic OA: a reasonable target for bone-acting agents." Nat Rev Rheumatol 9(8): 448-450.

12 Karsdal, M. A., et al. (2014). "The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments?" Annals of the Rheumatic Diseases 73(2): 336-348.

13 Ringe, J. D., et al. (2005). "Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate." Osteoporosis International 16(12): 2063-2068.

14 Laslett, L. L., et al. (2012). "Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial." Ann Rheum Dis 71(8): 1322-1328.

15 Cauley, J. A., et al. (2011). "Once-yearly zoledronic acid and days of disability, bed rest, and back pain: randomized, controlled HORIZON Pivotal Fracture Trial." Journal of Bone and Mineral Research 26(5): 984-992.

16 Reginster, J. Y., et al. (2013). "Strontium ranelate in the treatment of knee osteoarthritis: new insights and emerging clinical evidence." Therapeutic advances in musculoskeletal disease 5(5): 268-276.

17 Reginster, J. Y. (2014). "Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind randomised, placebo-controlled trial." Annals of the Rheumatic Diseases 73(2): e8.

18 Reginster, J. Y., et al. (2012). "Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial." Annals of the Rheumatic Diseases 72(2): 179-186.

19 Tan, Y. K. and P. G. Conaghan (2012). "Insights into osteoarthritis from MRI." International journal of rheumatic diseases 15(1): 1-7.

20 Guermazi, A., et al. (2013). "MRI-based semiquantitative scoring of joint pathology in osteoarthritis." Nat Rev Rheumatol 9(4): 236-251.

21 Roemer, F. W., et al. (2009). "Magnetic resonance imaging-based semiquantitative and quantitative assessment in osteoarthritis." Rheumatic Diseases Clinics of North America 35(3): 521-555.

22 Conaghan, P. G., et al. (2011). "Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group." Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 19(5): 606-610.

23 Bowes, M. A., et al. (2015). "A novel method for bone area measurement provides new insights into osteoarthritis and its progression." Annals of the Rheumatic Diseases. 74(3): 519-525.

24 Neogi, T., et al. (2013). "Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative." Arthritis and Rheumatism 65(8): 2048-2058.

25 Bowes, M. A. and P. G. Conaghan (2014). "Bone area demonstrates change in 3 months in a very small OA cohort." Osteoarthritis and Cartilage 22(suppl 1): 488.

26 Morko, J., et al. (2005). "Spontaneous development of synovitis and cartilage degeneration in transgenic mice overexpressing cathepsin K." Arthritis and Rheumatism 52(12): 3713-3717.

27 Schaller, S., et al. (2005). "In vitro, ex vivo, and in vivo methodological approaches for studying therapeutic targets of osteoporosis and degenerative joint diseases: how biomarkers can assist?" Assay Drug Dev Technol 3(5): 553-580.

28 Kraus, V. B., et al. (2011). "Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis." Osteoarthritis and Cartilage 19(5): 515-542.

29 Van Spil, W. E., et al. (2010). "Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria." Osteoarthritis and Cartilage 18(5): 605-612.

30 Pelletier, J. P., et al. (2015). "Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss." Annals of the Rheumatic Diseases 74(2): 422-429.

31 Reginster, J. Y., et al. (2013). "Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial." Annals of the Rheumatic Diseases 72(2): 179-186.

32 Hayami, T., et al. (2012). "Inhibition of cathepsin K reduces cartilage degeneration in the anterior cruciate ligament transection rabbit and murine models of osteoarthritis." Bone 50(6): 1250-1259.

33 Connor, J. R., et al. (2009). "Protective effects of a cathepsin K inhibitor, SB-553484, in the canine partial medial meniscectomy model of osteoarthritis." Osteoarthritis and Cartilage 17(9): 1236-1243.

34 McDougall, J. J., et al. (2010). "Cathepsin K inhibition reduces CTXII levels and joint pain in the guinea pig model of spontaneous osteoarthritis." Osteoarthritis and Cartilage 18(10): 1355-1357.

35 Hunter, D. J., et al. (2010). "Can cartilage loss be detected in knee osteoarthritis (OA) patients with 3-6 months' observation using advanced image analysis of 3T MRI?" Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 18(5): 677-683.

36 Hunter, D. J., et al. "Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score).[Erratum appears in Osteoarthritis Cartilage. 2011 Sep; 19(9):1168]." Osteoarthritis & Cartilage 19(8): 990-1002.

37 Heimann, T. and H. P. Meinzer (2009). "Statistical shape models for 3D medical image segmentation: a review." Medical Image Analysis 13(4): 543-563

38 Heimann, T., et al. (2007). "Automatic generation of 3D statistical shape models with optimal landmark distributions." Methods of Information in Medicine 46(3): 275-281.

39 Hunter, D. J., et al. (2010). "Can cartilage loss be detected in knee osteoarthritis (OA) patients with 3-6 months' observation using advanced image analysis of 3T MRI?" Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 18(5): 677-683.

40 Murphy, L. B., et al. (2010). "Estimating medical costs attributable to osteoarthritis in the US population: comment on the article by Kotlarz et al." Arthritis and Rheumatism 62(8): 2566-2567; author reply 2567-2568.

41 Hawker, G. A., et al. (2008). "Development and preliminary psychometric testing of a new OA pain measure-an OARSI/OMERACT initiative." Osteoarthritis Cartilage 16(4): 409-414.

42 Dougados, M., et al. (2000). "Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative." Osteoarthritis Cartilage 8(6): 395-403.

43 (2007). "User's Guide for the Measure of Intermittent and Constant Osteoarthritis Pain: ICOAP. Version 3. December 2007." from http://www.osteoarthritisresearch.ca/pdf/ICOAP-user-guide.pdf.

44 Hurst, N. P., et al. (1994). "Validity of Euroqol--a generic health status instrument--in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group." Br J Rheumatol 33(7): 655-662.

45 Brooks, R. (1996). "EuroQol: the current state of play." Health Policy 37(1): 53-72.

46 Harrison, M. J., et al. (2010). "Exploring the validity of estimating EQ-5D and SF-6D utility values from the health assessment questionnaire in patients with inflammatory arthritis." Health Qual Life Outcomes 8: 21.

47 Svarstad, B. L., et al. (1999). "The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence." Patient Educ Couns 37(2): 113-124.

12 APPENDICES

12.1 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	9.5	6	57
• Haematology	2	6	12
Pharmacokinetic samples	5	3	15
Blood samples for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics	19	1	19
Biomarker analysis	15	4	60
Additional unforeseeable samples			37
Total			**200**