STATISTICAL ANALYSIS PLAN

Medivir AB

Protocol 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

PAREXEL Study Number: 226198

Version: Final 1.0
Date: 22 June 2017

SIGNATURE PAGE - MEDIVIR

Declaration

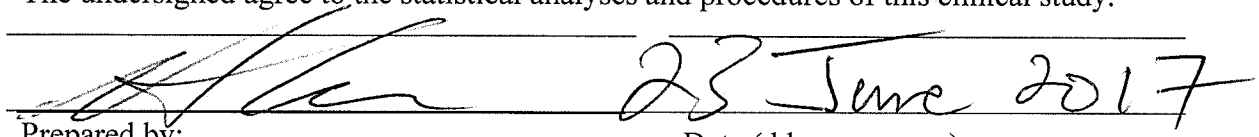
The undersigned agree to the statistical analyses and procedures of this clinical study.

	22-JUN-2017
John Öhd MD PhD Director Clinical R&D Medivir AB	Date (dd mmm yyyy)

SIGNATURE PAGE - PAREXEL

Delaration

The undersigned agree to the statistical analyses and procedures of this clinical study.



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Abbreviations and definitions

AE	Adverse event
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BML	Bone Marrow Lesions
CI	Confidence interval
CS	Clinically significant
CV	Coefficient of variation
ECG	Electrocardiogram
FAS	Full analysis set
h	Hour
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MOAKS	MRI Osteoarthritis Knee Score
NCS	Not clinically significant
NRS	Numeric Rating Scale
NK	Not known
OA	Osteoarthritis
PK	Pharmacokinetic
QOL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
t½	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TIC	Time Integrated Concentrations
Tmax	Time corresponding to occurrence of Cmax
WHO-DD	World Health Organisation - Drug Dictionary

1. Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is based on the final protocol, dated 09 September 2015 as well as all protocol amendments finalized including: amendment 1 dated 13 January 2016 and amendment 2 dated 20 July 2016. The SAP provides details on the planned statistical methodology for the primary and secondary analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures. It describes the safety and pharmacodynamic (PD) data, the handling of that data; the anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP covers the planned analysis to be conducted by PAREXEL of all safety and efficacy data as described in the protocol, and as collected in the source data.

2. Study Objectives and Hypotheses

2.1.1 Primary Objective

To assess the effect of MIV-711 on knee pain (at week 26), as measured by an 11-point numerical rating scale in patients with symptomatic and radiographic knee osteoarthritis

2.1.2 Hypothesis to be Tested

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

2.2 Secondary Objectives

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

Other secondary objectives include:

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

- *The effect of MIV-711 on worst target knee pain (1 week recall)
- The effect of MIV-711 on average contralateral knee pain (1 week recall)
- *The effect of MIV-711 on constant and intermittent OA pain
- *The effect of MIV-711 on global improvements in knee problem, knee pain and knee function
- *The effect of MIV-711 on knee joint OA symptoms (function, pain, stiffness)
- The effect of MIV-711 on global disease activity
- The effect of MIV-711 on quality of life (QOL)

- *The effect of MIV-711 on MRI bone area in regions other than primary region
- *The effect of MIV-711 on MRI bone marrow lesion volume
- *The effect of MIV-711 on MRI cartilage thickness loss
- The effect of MIV-711 in the semi quantitative MRI Osteoarthritis Knee Score (MOAKS) parameters
- *The effect of MIV-711 on patient reported e-diary daily recall knee joint pain
- The effect of MIV-711 on patient reported e-diary daily recall analgesics use
- The safety and tolerability of MIV-711
- The effect of MIV-711 on biomarkers for bone resorption (serum CTX-I) and for cartilage degradation (urine CTX-II) assessment

*Assessments on the target knee will be used to address these other secondary objectives.

2.3 Exploratory Objectives

In addition, the study will address the following exploratory objectives.

2.3.1 Biomarkers

- Assessment of the effect of MIV-711 on serum and urinary biomarkers of relevance for OA

- Serum CTXI and urine CTXII will be the only biomarkers covered in this SAP; all other biomarkers mentioned in the study protocol will not be included in this SAP.

- Baseline (visit 2) and steady state treatment (visit 8) blood and urinary samples will be stored for patients who sign a separate voluntary Informed Consent Form (ICF) for potential future pharmacogenomics and disease-related proteomic, genomics, metabolomics and lipidomics analyses, and will not be considered in this SAP.

The analysis of all serum biomarkers for: Procollagen type I N-terminal propeptide (sPINP), bone specific alkaline phosphatase (sBSAP), tartrate-resistant acid phosphatases (TRAP5b) will be described in a separate report (if analysed), and will not be considered in this SAP.

2.3.2 Pharmacokinetics

The pharmacokinetics and metabolism of MIV-711 and the relationship to patient factors and concomitant medications will be described in a separate report and will not be considered in this SAP.

3. Study Design

This is a multicentre, randomised, placebo-controlled, double-blind, three-arm parallel, Phase IIa study to evaluate the efficacy, safety and tolerability of MIV-711 in patients with symptomatic and radiographic knee OA. A total of 240 patients with knee OA meeting the eligibility criteria and who provide written informed consent will be randomised on a 1:1:1 basis to the intervention (MIV-711 low dose 100 mg or high dose 200 mg) or placebo. Six sites distributed in 6 European countries will be used to recruit patients.

Patients who are eligible and agree to continue with the study will return for the baseline visit within 30 days of the screening visit. After baseline assessments have been completed, patients will be randomised in a 1:1:1 ratio via a central secure 24-hour randomisation service to the intervention (MIV-711) arms or the placebo-controlled arm.

- Intervention arm I: Patients will receive a once-daily 100 mg oral dose of MIV-711 for 26 weeks in addition to their current medication.
- Intervention arm II: Patients will receive a once-daily 200 mg oral dose of MIV-711 for 26 weeks in addition to their current medication.
- Control arm: Patients will receive a once-daily oral dose of matching placebo for 26 weeks in addition to their current medication.

The study consists of a screening period of approximately 4 weeks (visit 1), a baseline assessment period at visit 2, a double-blind treatment period of visit 2 through visit 8, and a follow-up period of 4 weeks (visit 9) after the last dose of study treatment is administered. Study visits for clinical assessment and questionnaires will occur at visit 2 (baseline), visit 5, visit 6, and visit 8, regardless of treatment group. The end of the study is defined as the last visit (visit 9, week 30) of the last patient or, if applicable, when the last patient has rolled over to study MIV-711-202 and having finalized visit 2 of that study.

3.1 Study Endpoints

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) suggests that outcome measures for OA studies should include:

- Pain
- Function
- Quality of Life (QOL)

3.1.1 Primary Endpoint

The primary outcome variable is ‘Pain’ and will be measured using the change from

baseline in NRS "average" knee pain in the target knee with 7 days recall, between visit 2 (baseline) and visit 8, using a 0 to 10 NRS. The scale ranges from 0 indicating —"no pain", to 10 indicating —"pain as bad as it could be".

Other pain variables will include:

- worst target knee pain
- average contralateral knee pain
- constant and intermittent OA pain.

3.1.2 Secondary Endpoint

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

3.1.3 Other Secondary Endpoints

- *NRS e-diary assessment
- Analegsics use e-diary assessment
- *Bone Marrow Lesions (MOAKS)
- *Articular Cartilage (MOAKS)
- *Osteophytes (MOAKS)
- *Mean Cartilage thickness (Imorphics, Ltd.)
- *Combined Bone Marrow Lesion Volume (Imorphics, Ltd.)
- Patient Reported Outcomes: to assess for pain, function, disease activity, and QOL
- Laboratory assessments for blood and urine biomarkers (Serum CTXI and urine CTXII)

*These other secondary endpoints will be assessed for the target knee.

3.1.4 Safety Endpoints

- Adverse events
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Vital signs (blood pressure, pulse, and body temperature)
- 12-lead ECGs: PR interval, QRS interval, RR interval, QT interval, and QTc interval (Bazett's correction [QTcB], Fridericia's Correction [QTcF]), heart rate
- Concomitant medication

- Physical examination
- Rescue medication use

3.2 Study Population

The study population includes knee OA patients 40 to 80 years of age inclusive. The patient population fulfils the ACR criteria for OA and in addition must be radiographically confirmed as Kellgren and Lawrence (K-L) x-ray classification grade 2 or 3 and with a current average knee pain of greater or equal to 4 and less than 10 on a 1 to 10 NRS pain score. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

3.3 Sample Size Estimation

It is planned to recruit 240 patients at 6 centers in 6 countries for this study. Recruitment will be competitive across all 6 sites.

The distribution of patients across treatment groups will be as:

- MIV-711 100 mg: 80 patients
- MIV-711 200 mg: 80 patients
- Placebo: 80 patients.

Details of the formal sample size calculation are provided in the protocol Section 8.7.

3.4 Dose Administration

Patients will receive once-daily (OD) 100 mg or 200 mg oral dose of MIV-711, or placebo for 26 weeks in addition to their current medication. The IMP should be taken OD in the morning approximately 24 hours apart, before breakfast; breakfast can be taken approximately one hour later. The first dose is administered at the site during visit 2 (baseline). IMP should be dispensed during the visits and unused IMP returned by the patients for drug accountability at visit 5, visit 6, and visit 8. On days when the patient will visit the site the IMP must be taken at the site fasting (and not at home) and the time of the intake must be recorded in the source documents.

3.5 Randomization

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

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

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

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

3.6 Patient Replacement

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

Patients who withdraw from the study will not be replaced.

3.7 Trial Blinding

A double-blind/masking technique will be used.

3.8 Protocol Deviations

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

- Incorrect diagnosis
- Arthroscopy in the target knee during the study period
- Missing more than 5 doses of MIV-711 (based on accountability)

These criteria will be reviewed using blinded data prior to data analysis. Note: this is not an exhaustive list of deviations, these are only the deviations specified per protocol. The discussion during the BDRM will review all deviations collected at each site. All protocol deviations will be reviewed, evaluated and discussed between CRO and Sponsor before DBL.

3.9 Interim Analysis

No formal interim analysis that would allow early stopping of the study on the basis of demonstrating efficacy or futility is planned. Unblinded interim safety data (i.e. no efficacy analyses) will be reviewed during data monitoring committee (DMC) meetings held after 50, 100, 150 and 200 patients have completed visit 6.

3.10 Extension Protocol

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

4. Study Analysis Variables

4.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded at screening:

- Date of informed consent
- Medical and surgical history (including previous and current medical conditions and medications)
- Age calculated as (date of informed consent – date of birth)/365.25
- Gender
- Ethnic origin
- Race
- Height (cm)
- Body weight (kg)
- Body mass index (BMI) (kg/m^2)

4.2 Safety Variables

4.2.1 Adverse Events

All AEs and SAEs will be recorded in the eCRF system from the date the Informed Consent Form is signed (visit 1) until the safety follow up visit (visit 9) is completed.

4.2.2 Clinical Laboratory Tests

Blood samples for hematology and clinical chemistry, and urinalysis assessments will be collected during all study visits: Visit 1 (screening), Visit 2 (Week 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 14), Visit 7 (Week 20), Visit 8 (Week 26), and Visit 9 (Week 30, follow-up).

The following safety laboratory parameters will be measured:

Hematology: WBC and differential, % and absolute for: neutrophils, lymphocytes, monocytes, eosinophils, basophils; hemoglobin, hematocrit, RBC, RBC indices (MCV, MCH and MCHC) and morphology, platelet count

Chemistry: urea nitrogen, creatinine, calcium, sodium, potassium, bicarbonate, chloride, total protein, fasting glucose, total bilirubin, direct bilirubin and indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, CPK, CRP (at screening only), PTH (parathyroid hormone).

Urinalysis: with microscopic: specific gravity, pH, protein, glucose, ketones, nitrites, blood and leukocyte esterase

4.2.3 Other Laboratory Tests

- Post-menopausal determination at screening: Follicle stimulation hormone (FSH) in female patients.
- Urine Drug Screen measured at screening and Visit 5 (Week 8): Amphetamine, Benzodiazepines, THC, Cocaine, Oxycodone and Opiate.
- Serology Testing measured at screening: Hepatitis B surface antigen, total Hepatitis B core antibodies, antibodies to Hepatitis B Surface antigen, Hepatitis C virus, HIV 1 and 2.

4.2.4 Vital Signs

Vital signs (body temperature, heart rate, blood pressure, oxygen saturation) will be performed at all clinic visits prior to IMP dosing: Visit 1 (screening), Visit 2 (Week 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 14), Visit 7 (Week 20), Visit 8 (Week 26), and Visit 9 (Week 30, follow-up). All assessments will be collected in the supine position.

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

4.2.5 Electrocardiograms

A 12-lead ECG will be performed at all clinic visits. 12-lead serial ECGs will be recorded at visit 2 (baseline) pre-dosing and after 30 minutes, 1 hour and 2 hours post-dosing (± 10 minutes). Standard 12-lead ECG will be performed at all other visits 30 minutes after dosing (± 10 minutes).

The 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.

4.2.6 Physical Examination

A standard complete physical examination will be performed at visit 1 (screening), visit 2 (baseline), visit 5, visit 6 and visit 8.

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

4.2.7 Prior and Concomitant Medications

All concomitant medications taken during the study will be recorded with generic name, indication, daily dose, and start and stop dates of administration at each visit. For this study, prescription medicines, other than those prohibited by the study protocol are

permitted as concomitant medications to manage ongoing or chronic, stable medical conditions. Medications taken within 4 weeks of the screening visit will be documented as prior medication. Medication taken after the first dose of IMP will be documented as concomitant medication. Prior medications that are ongoing past Visit 2 IMP administration that involve a different dose level, frequency etc. from initial administration will be recorded as concomitant medication. Prior medications that are ongoing past Visit 2 IMP administration that do not involve a different dose level from initial administration will remain as prior medications.

The Brief Medication Questionnaire self-reported measure for the use of concomitant medication will be included at visit 5, visit 6, and visit 8.

4.2.8 Adherence to Study Medications

Patients will be asked to return any unused study medication at visit 5, visit 6, and visit-8 and drug accountability will be conducted.

4.2.9 Phone Call to Assess Safety and Tolerability

Follow-up telephone calls to assess safety and tolerability will occur 5 to 9 days after visit 2, visit 3, visit 4, visit 5, visit 6, and visit 7.

4.3 Pharmacodynamic Variables - Efficacy

4.3.1 Pain

The primary efficacy outcome variable is 'Pain' and will be measured using the change from baseline in the average pain score for the target knee, between visit 2 (baseline) and visit 8, using a 0 to 10 NRS. The scale ranges from 0 indicating —"no pain", to 10 indicating —"pain as bad as it could be".

4.3.2 MRI and Imaging

The key secondary endpoint will be the change from visit 2 (baseline) to visit 8 on MRI of bone area. A secondary endpoint of interest will be the change from visit 2 (baseline) to visit 8 on MRI cartilage thickness, and the volume of bone marrow lesions. Below are the denominations of the data items that will provide the basis for bone area and cartilage thickness and bone marrow lesion volume.

- MF_TAB: Area of bone in the medial femur region, MF
- CM_FEMUR_THCTAB: Average thickness of cartilage in the central medial femur region

- CM_TIBIA_THCTAB: Average thickness of cartilage in the central medial tibia region
- TOTAL_BML_VOLUME: Combined volume of all BML regions

Other secondary endpoints will include the analysis of MRIs using MOAKS scoring.

MRI assessment using MOAKS scoring will be used to assess the following features, as provided by PAREXEL MRI:

- Bone Marrow Lesions (BMLs) and cysts. This involves 15 subregions graded for BML size (including ill-defined lesion and cysts) measuring the total volume of the subregion occupied by BML(s). Grade 0= none, grade 1 < 33% of subregional volume, grade 2 = 33 to 66% of subregional volume and grade 3 > 66% of subregional volume.

- Articular Cartilage: This involves 14 articular cartilage regions graded for size of any cartilage loss (including partial and full thickness loss) as a percentage of surface area as related to the size of each individual region surface and percentage of loss in this subregion that is full-thickness loss.

- Osteophytes: This involves 12 sites scored for presence and size of osteophytes. Grade 0=none, Grade 1= small, Grade 2 = medium, Grade 3 = large.

The specific subregrions associated with the above three groups of MOAKS scoring are outlined in the table below:

Bone Marrow Lesions (BMLs) and cysts	**Articular Cartilage**	**Osteophytes**
Medial Patella	Medial Patella	Superior Patella
Lateral Patella	Lateral Patella	Inferior Patella
Medial Femur Trochlea	Medial Femur Trochlea	Medial Patella
Medial Femur Central	Medial Femur Central	Lateral Patella
Medial Femur Posterior	Medial Femur Posterior	Medial Femur Trochlea
Lateral Femur Trochlea	Lateral Femur Trochlea	Medial Femur Central
Lateral Femur Central	Lateral Femur Central	Medial Femur Posterior
Lateral Femur Posterior	Lateral Femur Posterior	Lateral Femur Trochlea
Medial Tibia Anterior	Medial Tibia Anterior	Lateral Femur Central
Medial Tibia Central	Medial Tibia Central	Lateral Femur Posterior
Medial Tibia Posterior	Medial Tibia Posterior	Tibia Medial
Subspinous	Lateral Tibia Anterior	Tibia Lateral
Lateral Tibia Anterior	Lateral Tibia Central	
Lateral Tibia Central	Lateral Tibia Posterior	
Lateral Tibia Posterior		

Bone Marrow Lesions (BMLs) and cysts: The 15 subregions will be assessed for:

- Size of BML
- Number of BMLs
- Percentage that is BML

Articular Cartilage: The 14 subregions will be assessed for:

- Size of any cartilage loss
- Percentage of Full Thickness Loss

4.3.3 Patient Reported Outcomes (PRO)

Patient-reported outcomes will be recorded using questionnaires at visit 2 (baseline) and at visit 5, visit 6, and visit 8. These PRO data will be used as measures of pain, function and disease activity.

4.3.3.1 NRS Scores - Knee Pain and Function in the Last Week

For the purposes of the questions below, the target knee is defined as the knee studied in this trial. Pain in your knee relates to any knee symptom you may experience for example pain or aching.

The scale ranges for NRS pain scores range from 0 indicating —"no pain", to 10 indicating —"pain as bad as it could be". The NRS scales will be used to assess for:

1) NRS question 1: NRSPTO (Primary Endpoint). On average, how would you rate the overall pain severity in your target knee over the last week (7 days)?

2) NRS question 2: NRSPAINW. How would you rate your worst pain severity in your target knee over the last week (7 days)?

3) NRS question 3: NRSPAINS. On average, how would you rate the overall pain severity in your other knee over the last week (7 days)?

4) NRS question 4: NRSACT. Over the last week (7 days), how active do you think your target knee arthritis has been?

5) NRS question 5: NRSSAT. Over the last week (7 days), how satisfied have you been with your target knee function?

For purposes of this SAP NRS question 4 refers to the patients "Global Assessment Score".

4.3.3.2 ICOAP Scores

Intermittent and constant osteoarthritis pain (ICOAP): an 11-item tool designed to assess constant and intermittent pain. Higher scores indicate worse constant and intermittent pain. The items assessed include:

- IP1- How intense has constant knee pain been
- IP2-Constant knee pain affecting sleep
- IP3-Constant knee pain - quality of life
- IP4-Frustrated by your constant knee pain
- IP5-Upset by your constant knee pain
- IP6-Intensity of pain that comes and goes
- IP7-Frequency pain that comes and goes
- IP8-Pain comes and goes affecting sleep
- IP9-Pain comes and goes quality of life
- IP10-Frustration pain that comes and goes
- IP11-Upset pain that comes and goes

4.3.3.3 WOMAC Scores

Western Ontario and McMaster Universities Osteoarthritis Index (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. Using an 11-box NRS scale, higher scores indicate worse pain, stiffness and physical function. Items assessed include:

- WOMAC1-Pain - walking on a flat surface
- WOMAC2-Pain - going up or down stairs
- WOMAC3-Pain - at night while in bed
- WOMAC4-Pain - sitting or lying down
- WOMAC5-Pain - while standing
- WOMAC6-Stiffness after first woke up in morning
- WOMAC7-Stiffness sitting or lying down
- WOMAC8-Difficulty - When going down the stairs
- WOMAC9-Difficulty - When going up the stairs
- WOMAC10-Difficulty - Getting up from a sitting
- WOMAC11-Difficulty - While standing

- WOMAC12-Difficulty - When bending to the floor
- WOMAC13-Difficulty - Walking on a flat surface
- WOMAC14-Difficulty - Getting in or out of a car
- WOMAC15-Difficulty - While going shopping
- WOMAC16-Difficulty - When putting on your socks
- WOMAC17-Difficulty - When getting out of bed
- WOMAC18-Difficulty - When taking off your socks
- WOMAC19-Difficulty - While lying in bed
- WOMAC20-Difficulty - Getting in or out of bath
- WOMAC21-Difficulty - While sitting
- WOMAC22-Difficulty - Getting on or off toilet
- WOMAC23-Difficulty - Performing heavy duties
- WOMAC24-Difficulty - Performing light duties

4.3.3.4 OMERACT Scores

Osteoarthritis Research Society International (OARSI)-OMERACT Responder index [2, 3] will be calculated using the WOMAC pain and function subscales and the patient‘s global assessment score. A responder will be defined as any subject that satisfies one of the following two overall conditions:

CASE 1. Improvement in pain or function ≥50% and absolute change ≥20

CASE 2. Improvement in at least two of the following conditions:
1. pain ≥20% and absolute change ≥10
2. function ≥20% and absolute change ≥10
3. patients‘ global assessment ≥20% and absolute change ≥10

Higher scores indicate worse pain, stiffness and physical function so that an “improvement” is only concerned with negative changes (or decreases) from baseline. Positive increases in scores relative to baseline suggest a worsening of pain (scores increasing over time suggests pain is increasing in severity over time).

4.3.3.5 Global Improvement Scores

Global improvements in knee problem, knee pain and knee function (Ability to use knee) recorded on a 6-point likert scale at visit 5, visit 6, and visit 8 only: (completely better, much better, better, no change, worse, much worse)

4.3.3.6 Quality of Life

At visit 2 (baseline) and visit 8: EuroQol -5 Dimensions (EQ-5D-5L) - a generic measure of self-reported health status. Items assessed include:

- Usual Activities
- Anxiety/Depression
- Self-Care
- Pain/Discomfort
- Mobility
- Health Rating

4.3.3.7 Brief Medication Questionnaire

The Brief Medication Questionnaire is a self-reported measure for the use of concomitant medication and will be administered at visit 5, visit 6, and visit 8. Items assessed include:

- How much did you take each time
- How many days did you take it
- The dosage times are inconvenient
- How many times per day did you take it
- It is hard to get my refill on time
- How many times did you miss taking it
- It is hard to open the container
- Hard to read the print on the container
- For what reason were you taking it
- It is hard to remember all doses
- Stop taking meds since(V5) or (V6, V8)
- Medication Name

4.3.3.8 E-Diary Assessnment of NRS and Analgesic Use

In an e-diary format, a patient knee pain diary (NRS) and analgesia questionnaire will be completed daily every 12 hours (AM, PM) during three two-week periods prior to visit 2 (baseline), visit 6 and visit 8. Baseline will be defined as the last observation prior to the first dose of investigational product. The assessments in the e-diary comprise:

- Average overall knee pain severity in the target knee over the past 12 h (0 -10 NRS)
- Adherence to usual analgesics regimen:
    - Has patient taken any pain medication over last 12 hours? (Yes, No).

- Classify your pain medication usage over the last 12 hours: (More than normal, Normal, Less than normal)

- Intake of IMP (note: the e-diary device is kept by the patients for the full duration of the study, intake of IMP will be registered daily throughout the study)

4.3.4 Secondary Efficacy Parameters

4.3.4.1 Biomarkers

Secondary Endpoints: Blood and urine samples for the analysis of secondary and exploratory bone and cartilage markers of relevance for OA disease for analysis of serum CTX-I and urinary CTX-II biomarkers will be taken at visit 2 (baseline) and visit 4, visit 6, visit 8, and visit 9.

- urinary CTX-II biomarkers
- serum CTX-I

4.3.4.2 Other Imaging Assessments

K-L scoring based on target knee radiographs no older than 12 months is required to assess inclusion criterion 3.

At visit 2 (baseline) and visit 8, MRI acquisition will be performed on the target knee for measurement of bone area, cartilage thickness and BML volume.

4.4 Analysis Populations

4.4.1 Intent-to-Treat Population (ITT)

All randomised patients in the treatment group to which they were randomised, regardless of whether treatment was received as planned.

4.4.2 Modified Intent-to-Treat Population (mITT)

mITT is the full analysis set (FAS) consisting of all patients having both a baseline and at least one post-baseline value for the primary variable (NRS pain score).

4.4.3 Per Protocol Population (PPS)

Those patients who adhered to the treatment regimen of the program to which they were allocated, provided sufficient assessment of primary outcomes, and did not violate the study protocol in any substantial way.

4.4.4 Safety Analysis Population (SAF)

The safety analysis population will include all patients receiving at least one dose of either MIV-711 or placebo. These patients will be analyzed according to treatment actually received.

5. General Considerations for Data Presentations

In this study IMP refers to any amount of the treatments defined in section 3.4, regardless of the time or period of administration.

Data for all enrolled patients who receive at least one dose of IMP will be presented in the data listings.

A patient who is enrolled but does not receive IMP will be included in those data listings for which they have data but will be excluded from all data summaries. Data summaries will only include those patients that receive IMP.

For those listings or data summaries where baseline and change from baseline measurements will be presented, unless stated otherwise, the baseline assessment to be used for calculating change from baseline will be the last valid assessment prior to first dose administration.

All pre- and post-dose assessments including unscheduled assessments will be included in the data listings. For unscheduled assessments collected pre-dose, the last assessment taken for a time point will be used in the data summaries (summary tables, figures, and statistical analysis); for all post-dose time points, the original assessment for any given time point will be used in the data summaries (summary tables, figures, and statistical analysis).

For summaries of safety data continuous variables will be summarized using descriptive statistics including: number of observations (n), mean (arithmetic), median, standard deviation (SD), minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. In summaries for safety the denominator for all percentages will be the number of patients in a given treatment group.

Safety and efficacy data that are reported as missing will be excluded from all descriptive and non-descriptive data analysis. There will be no imputation of any data. Observations that might be considered spurious (extreme relative to the majority of the data) will not be altered or removed from any presentation of the data, including the calculation of summary statistics (means, medians, etc.), unless approved by the sponsor.

For data listings, all raw data will be reported/displayed exactly as provided. For summaries of quantitative safety data, the minimum and maximum value will be reported exactly as the raw data are reported; measures of central tendency (means, medians) will be reported to one more decimal place than the raw data; measures of variance (SD) will be reported to two more decimal places than the raw data.

Unless stated otherwise there will be no adjustment for multiple comparisons. All statistical tests will be one-sided and will be performed at the 5% level of significance (Type I error =0.05).

In all data persentations 'Treatment' will be defined as consisting of the three protocol defined categories: 200 mg, 100 mg, placebo. Listings will include all patients and will be sorted by treatment, patient number, and time point (where applicable). In all listings treatment will be grouped in the order: 200 mg, 100 mg, placebo. All derived data used in a data summary or statistical analysis will be listed.

5.1 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) (SAS® Institute Inc., Cary, North Carolina, United States of America [USA]) Version 9.2 or higher.

6. Patient and Treatment Information

6.1 Patient Disposition

The completion status, date of completion or discontinuation, the reason for discontinuation, and the study day of withdrawal will be listed. The number of patients enrolled and the frequency and percentage of patients completing the study, patients withdrawing early, and primary reason for withdrawal will be summarized by treatment and overall. Also included in this summary will be the numbers of patients in each of the analysis populations: ITT, mITT, PPS.

Per protocol patients will take IMP until V8 and then they have a safety follow up visit (V9) 4 weeks after last IMP dose. If a patient is withdrawn IMP is stopped but the patient

is still asked to come for the safety follow up visit (V9) 4 weeks after last IMP. Some patients are withdrawn but refuse or are unable to attend the safety follow up visit (V9) 4 weeks later.

6.2 Patients Excluded from Analysis Populations

Each patient excluded from one of the analysis populations will be listed along with the reason for their exclusion.

6.3 Eligibility Criteria

All enrolled patients who did not meet an inclusion criterion and all enrolled patients who met an exclusion criterion will be listed.

6.4 Exclusion Tests

Results of the exclusion tests will be listed. These will include laboratory tests performed prior to dosing for: FSH testing, serology, and urine drug screen.

6.5 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 may lead to the exclusion of a patient from the Per Protocol Set (PPS). Deviations will be defined prior to unblinding. All reported protocol deviations will be listed.

6.6 Demographic Data

Demographic and baseline characteristics will be evaluated for the ITT and for the PPS. Demographic information will be listed. Descriptive statistics will be obtained for the continuous variables: height, age, BMI, and body weight and presented overall. Frequencies and percentage of patients will be tabulated for the categorical variables ethnicity, race, and gender.

6.7 Medical History

Medical and surgical history data recorded prior to dosing will be listed for each patient. Medical history will be coded using the MedDRA (Version 18.1).

Only those body systems where a condition or abnormality has been reported will be listed.

6.8 Prior and Concomitant Medication

Prior and concomitant medications will be coded using WHO Drug (September 2015 version). These medications will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Prior and Concomitant Medications will be listed by patient.

Summary tables of the number of percentage of patients by treatment and ATC classification will be provided for prior and concomitant medications.

6.9 Dose Administration

Information collected per the dose administration CRF will be listed including patient number, treatment, visit, and the date and time of administration as well as the dose form, route of administration, number of capsules dispensed and number of capsules returned.

The number and percentage of patients who received IMP will be summarized for each on site visit and by treatment. Descriptive statistics will be used to summarize drug accountability as the number of capsules returned for each on site study visit by treatment.

Compliance will be derived as the number of days patient was exposed to IMP. 100% compliance will be considered for dosing during the period Visit 2 to Visit 8.
The number of capsules used will be derived as the number of capsules dispensed minus the number of capsules returned. Subjects with less than 100% compliance will be identified among those who have results for “Reason not all unused Capsules returned”.

7. Pharmacodynamic Analysis - Efficacy

The primary and secondary efficacy analysis will be based on the mITT population.

7.1 NRS Pain Data

NRS data for knee pain will be listed for each patient, treatment, and time point. NRS results will be shown for the following:

- Primary endpoint: Amount of pain severity in the target knee last week (SDTM: Overall pain severity in target knee

- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

Change from baseline will be derived for each of the above NRS pain scores. These changes from baseline scores will be descriptively summarized by visit and treatment. Frequency tables by treatment will be used to summarize the number and percent of patients in each of the categories observed for:

- Duration of Knee Pain Past 12 Months: Within the last 7 Days, Days 8-30, Days 31-92, More than 92 Days
- Onset of Knee Pain: Within the last 12 months, 1 to 5 years, 5 to 10 years, More Than 10 years

Results for duration and onset of knee pain will be listed for each patient.

Graphical presentation of the observed and change from baseline NRS pain scores will include:

- Mean ± 95% CI Profiles of Observed NRS Scores by Treatment, mITT Population
- Mean ± 95% CI Profiles of Change From Baseline NRS Scores by Treatment, mITT Population

7.2 Statistical Analysis of the NRS Pain Data

To assess the sensitivity of the statistical analysis to the choice of analysis set, the primary efficacy analysis described below will be considered for both the mITT and the PPS populations.

The primary hypothesis of this study is that MIV-711 will reduce pain in patients with moderate knee osteoarthritis diagnosed based on symptomatic and radiologic criteria. To statistically test this hypothesis, a linear mixed model via SAS PROC MIXED based on the FAS (mITT). The model will include fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. The baseline NRS score will be included as a covariate for adjustment.

Patients considered pain medication users at baseline will be identified via concomitant medication analgesic usage. Pain medication users will include any patient exposed to a prescribed analgesic at time of first IMP intake and the medication was ongoing at the time of visit 2.

The dependent variable in the linear model is the change from baseline NRS pain score. Separate mixed model analyses will be considered for each of the change from baseline NRS pain scores.

- Primary endpoint: Amount of pain severity in the target knee last week (SDTM: Overall pain severity in target knee
- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

In this analysis the contrast of primary interest is the treatment difference (active versus placebo) at visit 8 week 26. LSmeans at visit 8 for the change from baseline score will be reported from the mixed model. LSmeans for the overall effect of treatment, estimates of the pair-wise treatment differences, two-sided 95% confidence intervals (CI), and p-value (one-sided) will be provided.

The following SAS code maybe used as reference:

```
PROC MIXED data=;
CLASS patient  treatment week;
MODEL NRS_chg= NRS_baseline treatment week treatment*week baseline_conmed_pain_use/
DDFM=KR ;
RANDOM site ;
REPEATED week / SUBJECT=patient TYPE=UN;
LSMEAN treatment*week  treatment / diff CL ALPHA=0.1  ;
RUN;
```

In an alternate sensitivity analysis of the primary endpoint (Amount of pain severity in the target knee last week) that could be considered as applicable, the linear model described in this section would include the PRO for e-diary analgesic use (Yes, No) as an additional independent factor. This analysis would be considered only if baseline pain medication usage could not be adequately identified via the concomitant medication records. The effect of whether or not a patient was an analgesic user at baseline as defined by the e-diary would then be considered as the additional factor.

7.2.1 Multiplicity Adjustment for the Primary Endpoint

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

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

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

7.2.2 Visualizations for the Primary Endpoint

Mean profiles for treatments (MIV-711) will be compared with placebo for each treatment as well as the difference from placebo treatment, as obtained from the change from baseline NRS score estimated least squares means. The difference from placebo in least squares means obtained from the above mixed model (section 7.2) will be presented in the following figures:

- NRS Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, mITT Population
- NRS Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, PPS Population

7.3 Key Secondary Analysis: MRI of Bone Area in Target Knee

The observed and change from baseline of the MRI of the bone area of the medial femur for the target knee will be listed for each patient and descriptively summarized by treatment and visit.

7.3.1 Statistical Analysis of the MRI of Bone Area in Target Knee

As the key secondary analysis of efficacy, the change from baseline in the MRI of bone area in the target knee will be analysed using the same statistical model described in

Section 7.2 above. This analysis will be based on the mITT population. Results will be summarized.

Mean profiles for treatments (MIV-711) will be compared with placebo by plotting the difference from placebo using the change from baseline MRI bone area score:

- MRI of Bone Area Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, mITT Population

7.4 Secondary Analysis: MRI of Cartilage Thickness in Target Knee

The observed and change from baseline of the MRI of the cartilage thickness for the target knee will be listed for each patient and descriptively summarized by treatment and visit. Source data for these analyses will be obtained from:

- CM_FEMUR_THCTAB: Average thickness of cartilage in the central medial femur region
- CM_TIBIA_THCTAB: Average thickness of cartilage in the central medial tibia region

7.4.1 Statistical Analysis of the MRI of Cartilage Thickness in Target Knee

As a secondary analysis of efficacy, the change from baseline in the MRI of cartilage thickness in the target knee will be analysed using the same statistical model described in Section 7.2 above. This analysis will be based on the mITT population. Results will be summarized.

Mean profiles for treatments (MIV-711) will be compared with placebo by plotting the difference from placebo using the change from baseline MRI cartilage thickness score:

- MRI of Cartilage Thickness Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, mITT Population

7.5 Secondary Analysis: MRI of total BML Volume in Target Knee

The observed and change from baseline of the MRI of the total bone marrow lesion volume for the target knee will be listed for each patient and descriptively summarized by treatment and visit. Source data for these analyses will be obtained from:

- Total_BML_Volume

7.5.1 Statistical Analysis of the MRI of Total BML Volume in Target Knee

As a secondary analysis of efficacy, the change from baseline in the MRI of total bone marrow lesion volume in the target knee will be analysed using the same statistical model described in Section 7.2 above. This analysis will be based on the mITT population. Results will be summarized.

Mean profiles for treatments (MIV-711) will be compared with placebo by plotting the difference from placebo using the change from baseline MRI cartilage thickness score:

- MRI of Total BML Volume Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, mITT Population

7.6 Analysis of Other Secondary Imaging Assessments

Other secondary imaging variables will be listed for each patient and descriptively summarized by treatment and visit. These other secondary imaging variables will include:

MOAKS Variables

- Bone Marrow Lesions (BMLs) and cysts
  - Size of BML: 0=’None’, 1=’<33%’, 2=’33-66%’, 3=’>66%’,9=’Not Evaluable’
  - Number of BMLs: scored 9 to 99
  - Percentage that is BML: 0=’None’, 1=’<33%’, 2=’33-66%’, 3=’>66%’, 9=’Not Evaluable’

- Articular Cartilage
  - Size of any Cartilage Loss: 0=’Normal’, 1=’<10% Area’, 2=’10-75% Area’, 3=’>75% Area’, 9=’Not Evaluable’
  - Percentage Full Thickness Loss: 0=’Normal’, 1=’<10% Region’, 2=’10-75% Region’, 3=’>75% Region’, 9=’Not Evaluable’

- Osteophytes: 0=’None’, 1=’Small’, 2=’Medium’, 3=’Large’, 9=’Not Evaluable’

For the MOAKS imaging variables collected quantitatively the change from baseline score will be derived and descriptively summarized by treatment and visit. For MOAKS variables with categorical response, the number and percentage of subjects in each treatment for each category will be summarized.

7.7 Analysis of Other Patient Reported Outcomes (PROs)

7.7.1 Intermittent and Constant Osteoarthritis Pain (ICOAP) Knee Version

The observed raw ICOAP scores will be listed by treatment and visit for each patient.

The observed results for the intermittent and constant osteoarthritis pain (ICOAP) score will be transformed to a 0-100 scale for analysis. The following methods will be used to transform the ICOAP scores:

Constant pain subscale

To calculate the Total constant pain subscale, sum the scores within each time point for items IP1 through IP5. Maximum constant pain score ranges from 0 to 20.
This score can be transformed to a score out of 100 using the following formula:

(Total constant pain score / 20) x 100

Intermittent pain subscale

To calculate the total intermittent pain subscale, sum the scores within each time point for items IP6 through IP11. Maximum intermittent pain subscale ranges from 0 to 24.
This score can be transformed to a score out of 100 using the following formula:

(Total intermittent pain score / 24) x 100

Total pain score

To calculate the total ICOAP score, sum the constant and intermittent pain subscales within each time point. Maximum total pain score ranges from 0 to 44.
This score can be transformed to a score out of 100 using the following formula:

(Total pain score / 44) x 100

The three transformed ICOAP scores (Constant Pain, Intermittent Pain, and Total Pain) will be listed by patient for each scheduled time point. Change from baseline will be derived for each of these transformed ICOAP scores. The observed and change from baseline values for these three transformed ICOAP scores will be listed and the change from baseline values will be descriptively summarized by treatment and time point. Figures of the mean change from baseline ICOAP response, using each transformed ICOAP score, will be used to visualize the behavior of the ICOAP response over time:

- ICOAP Change From Baseline by Treatment and Time Point, mITT Population

7.7.2 Analysis of the WOMAC

The observed WOMAC scores for pain, stiffness, and physical function will be listed. Change from baseline scores will be derived for each WOMAC item, listed by patient and descriptively summarized by treatment and visit.

Mean profiles for treatments (MIV-711) will be compared with placebo by plotting the change from baseline WOMAC score:

- WOMAC Pain Score Mean Change From Baseline (95% CI) by Treatment and Time Point, mITT Population.
- WOMAC Stiffness Score Mean Change From Baseline (95% CI) by Treatment and Time Point, mITT Population
- WOMAC Difficulty Score Mean Change From Baseline (95% CI) by Treatment and Time Point, mITT Population

7.7.3 (OARSI)-OMERACT Responder Criteria

The following steps will be used to derive OARSI-OMERACT response (Yes, No). This analysis will use the PROs from the WOMAC pain data, the WOMAC Function data, and the patient global assessment NRS observed at Visit 2 and Visit 8. It is expected Visit 8 will be the last 'on-treatment' visit for each subject.

Step 1. Derive Total Scores:

a) Total WOMAC Pain (Sum of 5 questions): For each subject and each scheduled time point derive a total score by summing over all 5 pain responses. For each subject this will provide a total WOMAC Pain score out of 50 for each protocol scheduled time point. Denote this new variable in the data set as 'WOMAC_Pain_50'.
b) Total WOMAC Function (Sum of 17 questions): For each subject and each scheduled time point derive a total score by summing over all 17 difficulty responses. For each subject this will provide a Total WOMAC Function score out 170 for each protocol scheduled time point. Denote this new variable in the data set as 'WOMAC_Func_170'.
c) Patient Global Assessment (NRS question 4: Over the past week, how active do you think your knee arthritis has been?). Use this score as is, scored out of 10.

Step 2. Transform the three scores from Step 1 to create three new scores, each out of 100:

a) Transformed WOMAC Pain Score:
WOMAC_PAIN_100 = WOMAC_Pain_50 ☒ 2.

b) Transformed WOMAC Function Score:
WOMAC_FUNC_100 = WOMAC_Func_170 ÷1.7.
c) Transformed Global Assessment Score:
NRSACT_100 = (Global Assessment Score) ☒ 10.

Step 3. Comparing Visit 8 against Visit 2: Use the transformed scores from step 2 to derive change between baseline and percentage change from baseline scores.

Denote the change from baseline scores as:

- CHG_WOMAC_PAIN_100
- CHG_WOMAC_FUNC_100
- CHG_NRSACT_100

Denote the percentage change from baseline scores as:

- PCHG_WOMAC_PAIN_100
- PCHG_WOMAC_FUNC_100
- PCHG_NRSACT_100

Percentage change from baseline will be calculated as:
((Visit 8 Score – Visit 2 Score) ÷ Visit 2 Score) ☒ 100

The total scores and the transformed scores for each of WOMAC pain, WOMAC physical function, and global assessment will be listed by patient and visit along with their change from baseline scores and percentage change from baseline scores. Change from baseline scores will be presented for Visit 8 only. Percentage change from baseline scores will be derived from visit 2 and visit 8 data only.

Step 4. Derive Responder OARSI-OMERACT (Yes, No): In all derived scores, low values are associated with less severe pain (0 = no pain) and high scores are associated with more severe pain (100 = worst pain). In assessing for a positive OMERACT response, patient improvement (Response = Yes) is associated with decreases (negative changes) from baseline and (negative) percentage (changes) decreases from baseline. The different criteria are quantified in the tables below.

Case 1: using the change from baseline and percentage change from baseline scores for WOMAC pain and WOMAC function (from step 3), an OMERACT responder will be flagged as 'Yes' if either of the following 2 criteria are satisfied:

Criteria		**Decrease from Baseline**		**Percentage Decrease from Baseline**	**OMERACT Responder**

1	WOMAC Pain	≥ 20	and	≥ 50%	Yes
2	WOMAC Function	≥ 20	and	≥ 50%	Yes

Case 2: using the change from baseline and percentage change from baseline scores for WOMAC pain, WOMAC function, and global assessment score (from step 3), an OMERACT responder will be flagged as 'Yes' if at least 2 of the following 3 criteria are satisfied:

Criteria		**Decrease from Baseline**		**Percentage Decrease from Baseline**	**OMERACT Responder**
3	WOMAC Pain	≥ 10	and	≥ 20%	Yes
4	WOMAC Function	≥ 10	and	≥ 20%	Yes
5	Global Assessment NRS	≥ 10	and	≥ 20%	Yes

A subject is a 'Yes' responder if either of criteria 1 or 2 are satisfied. If neither criteria 1 or 2 are satisfied, criteria 3, 4 and 5 will be checked.

A listing will be created that presents each patient's responder status by treatment. Included in this listing will be the associated change from baseline and percent change from baseline values.

The number and percentage of subjects with responder status will be summarized by treatment.

7.7.4 **Global Improvements**

Global improvements in knee problem, knee pain and knee function that were recorded on a 6-point likert scale: completely better, much better, better, no change, worse, much worse.

Descriptive tables will be used to summarize the number and percentage of each global improvement response for each treatment group by time point. All data will be listed for each patient.

7.7.5 **Quality of Life PRO – EQ-5D-5L**

Observed results from the EQ-5D-5L will be listed for each patient.
This will include results from the 5 dimensions: mobility; self-care; usual activity; pain or discomfort; and anxiety or depression, in addition to the reported health rating score.

Change from baseline scores will be derived for each QOL response as Visit 8 Week 26

versus Visit 2 Day 1. The change from baseline scores will be summarized using descriptive statistics by treatment group. The observed mean scores with 95% CI will be plotted by treatment and time point to visualize the QOL response over time.

7.7.6 **E-diary for Patient Pain**

All data collected in e-diary format, will be listed for each patient.
Data permitting summary tables by treatment and time point will be provided for the e-diary information reported for NRS scores and pain medication usage.

Separate summary tables will be provided for AM and PM response as well as a table for overall 24 hour response. The overall summary will use the mean of the AM and PM NRS scores provided for each visit, to obtain one record for that visit.

The number and percentage of patients with 'Yes/No' response to pain medication usage on the e-diary will be provided separately for AM, PM as well as for 24 hours overall. For the overall table, at least one 'Yes' response, either for the AM or the PM response, will be interpreted as a 'Yes' response over the 24 hours.

The number and percentage of patients with each pain medication usage response ('More than Normal', 'Normal', 'Less than normal') will be summarized by treatment and visit, with separate summaries for AM and PM response.

Data permitting the average NRS e-diary score will be visualized using a plot of mean NRS response by treatment and time point. Separate figures will be provided for the AM and PM NRS scores as well as overall 24 hours for each visit. For the overall figure the mean of the AM and PM NRS scores will be used to obtain 1 record at each visit prior to computing descriptive statistics.

7.7.7 **Biomarkers from Serum and Urine Samples**

The serum CTX-I and urinary CTX-II biomarkers will be presented in data lisitngs by subject and time point and in descriptive summary tables by treatment and time point. Figures of mean response over time with +/- 95% CI will be used to visualize their distribution over time for each treatment.

Time-Integrated-Concentrations (TIC) will be derived for each serum CTX-I and urinary CTX-II biomarkers. For each biomarker the mean TIC value and the standard deviation (SD) of the TIC will be derived. For each biomarker a Z- score will be derived by subtracting the mean and dividing by SD. TIC results and associated Z-scores will be listed for each subject.

8. Safety Analysis

All safety analyses will be based upon the SAF. If one or more patients received incorrect IMP, these data will also be presented for the SAF.

8.1 Adverse Events

All AEs reported will be coded and classified according to MedDRA version 18.1.

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

Non-treatment emergent adverse events (NTEAE): AEs that occurred before the administration of IMP and did not worsen in severity or relationship after exposure to IMP.

All AE data as captured on the CRF will be listed by patient. All serious AEs (SAEs) will be listed. A listing of all AEs leading to treatment discontinuation will be presented.

Unless specified otherwise, all adverse event summaries will include the TEAEs only and adverse event summary counts of AEs will be the number of patients reporting adverse events and not the number of events reported. The number and percentage of patients with adverse events will be tabulated by body system and preferred term for each treatment. A patient with multiple adverse events within a body system is only counted once towards the total of that body system. If the same AE (preferred term) is reported several times for the same patient, it will only appear once for that specified treatment in the summary tables.

For patients with multiple adverse events of the same preferred term and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity.

Presentations of AEs (tables and listings) will be by treatment defined by the dose level of MIV-711 and placebo.

A general summary of all treatment-emergent adverse events will show the number and percentage of patients, as well as the number of events, according to the following categories:

- All treatment emergent adverse events
- ‘Related’ treatment emergent adverse events
- Mild treatment emergent adverse events
- Moderate treatment emergent adverse events
- Severe treatment emergent adverse events

- Serious treatment emergent adverse events
- Treatment emergent adverse events leading to early termination
- Deaths

Other summary tables for adverse events will include:

- Number and Percentage of Patients with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment
- Number and Percentage of Patients with Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, Severity, and Treatment.
- Number and Percentage of Patients with Treatment Emergent Adverse Events 'Not Related to IMP' by System Organ Class, Preferred Term, Severity, and Treatment.
- Number and Percentage of Patients with Serious Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment
- Number and Percentage of Patients with Treatment Emergent Adverse Events Leading to Discontinuation by System Organ Class, Preferred Term, and Treatment

8.2 Clinical Safety Laboratory Tests (Hematology, Chemistry, Urinalysis)

8.2.1 Hematology and Chemistry

A by-patient listing of all observed chemistry and hematology laboratory data will be provided. Laboratory results outside the normal range will be flagged. The abnormal values will be flagged with 'L' (low) for values below the lower limit of the laboratory's normal range or 'H' (high) for values above the upper limit of the laboratory's normal range. Abnormal values will be graded as not clinically significant (NCS) or clinically significant (CS). Clinically significant laboratory results will be included in the AE listings.

The observed values of all safety laboratory assessments for clinical chemistry and hematology will be summarized using descriptive statistics showing the number of observations (n), mean, median, SD, minimum, and maximum value. Table summaries will be presented by treatment and time point.

Baseline values for all clinical chemistry and hematology parameters will be categorized as being below the normal range (Low), within the normal range (Normal), and above the normal range (High). Shift from baseline tables will present the frequency and percentage of patients who have observations that are Normal, Low, or High. Shift tables will be presented by treatment group for values shifting from Day -1 to the maximum and the minimum post-dose value.

All hematology, chemistry, and coagulation, laboratory parameters noted in Section 4.2.2 of this SAP will be tabulated.

8.2.2 Urinalysis

Urinalysis test results will be listed. All positive findings in the microscopic examination will be listed.

Observations outside the normal range will be flagged. The abnormal quantitative values will be flagged with 'L' for values below the lower limit of the laboratory's normal range, 'H' for values above the upper limit of the laboratory's normal range, or 'Ab' for abnormal qualitative test results. All original and unscheduled assessments will be listed.

8.3 Other Blood and Urine Samples

Details of the other blood and urine sample collections collected for pharmacogenomics, proteomics, genomics, metabolomics and lipidomics will be listed for each patient.

8.4 Vital Signs

The observed data for blood pressure (systolic and diastolic), heart rate (pulse), pulse oximetry, and body temperature will be listed by patient, and time point. Change from baseline values for blood pressure (systolic and diastolic), and heart rate (pulse) will be derived and listed. The baseline value to be used to derive change from baseline will be last assessment prior to first dose on Visit 2. The overall qualitative assessment for vital signs will be listed.

For systolic and diastolic blood pressure and heart rate, the observed values and change from baseline data will be summarized by treatment and time point. Table summaries will include descriptive statistics showing the number of observations (n), mean, SD, median, minimum, and maximum value.

8.5 12-Lead Safety ECG

Observed quantitative results for RR, PR, QRS, QT, QTcB (corrected QT according to Bazett), QTcF (corrected QT according to Fridericia) and heart rate will be listed for each patient. Change from baseline for QT, QTcB, QTcF will be derived and listed.

In the calculation of change from baseline, the baseline value for each period will be the last assessment prior to first dose on Visit 2.

The overall qualitative ECG assessment Abnormal NCS, Abnormal CS, and any comments will be listed for each patient.

For QT, QTcB, QTcF the observed and change from baseline data will be summarized by treatment and time point. Summaries will include tables of descriptive statistics showing the number of observations (n), mean, SD, median, minimum, and maximum value.

The number and percentage of patients having observed QT, QTcB, QTcF values that satisfy the following conditions will be summarized by treatment and time point:

- ≤ 450 msec
- 450 < to ≤ 480 msec
- 480 < to ≤ 500 msec
- > 500 msec

The number and percentage of patients having change from baseline QT, QTcB, QTcF values that satisfy the following conditions will be presented by treatment and time point:

- ≤ 0 msec
- > 0 to ≤ 30 msec
- > 30 to ≤ 60 msec
- > 60 msec

8.6 Physical Examination and Weight

All abnormal physical exam findings (pre and post-dose assessments) will be listed.

Patient weight collected pre and post dose will be listed.

8.7 Phone Call to Assess Safety

Results of this assessment will be listed for each patient and each visit.

9. Reporting Output

The following details the requirements and specifications for the presentation of the tables, figures and listings (TFLs) as set out in the TFL shells.

The tables, listings, figures and any non-descriptive statistical analysis will be produced using Unix SAS® Software (Version 9.2 or higher). The REPORT procedure will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

Tables, listings, and figures will be produced in the order that they appear in the textual sections of the plan.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 8pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins: top, left, right, and bottom: 1 inch). Details are provided below.

- A separate RTF document will be created for each table, figure and listing individually.
- All TFLs will be produced in a landscape format, as far as is feasible.
- The standard font size and font type are "8 point", "Courier New" for all TFLs.
- Every page of each output will contain a footer indicating the date and time when the output was produced.
- Page numbering of tables and listings will use the format "Page X of Y". Page numbering for figures will be consecutive integers.
- The ordering of visits will be chronological
- Footnotes are left justified.

10. References

1. 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 25672568.

11. Summary Tables

TLF Number	Title	Topine Item
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Table 14.1.2.2	Demographics – Continuous Variables, mITT Population	
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Table 14.1.3.2	Demographics - Categorical Variables, mITT Population	
Table 14.1.4.1	Prior Medications, PPS Population	
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Table 14.1.5.2	Concomitant, mITT Population	
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TLF Number	Title	Topline Item
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Figure 14.2.3.3	NRS Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, mITT Population	Yes
Figure 14.2.3.4	NRS Change From Baseline (LSMean Difference ± 95% CI) Difference from Placebo by Treatment and Time Point, PPS Population	Yes
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13. Listings

TLF Number	Title	Topline Item
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Listing 16.2.1.3	Enrolled Patients Who Did Not Meet All Eligibility Criteria	Yes
Listing 16.2.1.4	Exclusion Tests	Yes
Listing 16.2.2.1	Protocol Deviations	Yes
Listing 16.2.4.1	Demographics	Yes
Listing 16.2.4.2	Medical History	
Listing 16.2.5.1	Prior and Concomitant Medications	Yes
Listing 16.2.5.2	Dose Administration	Yes
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14. Table Shells

Table 14.1.1
Patient Disposition
All Enrolled Patients

	Treatment			
	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
Number Patients Enrolled	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Completed Study	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Discontinued from Study	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Number Patients in ITT Population	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Number Patients in mITT Population	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Number Patients in PPS Population	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Number Patients in SAF Population	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Reason for Discontinuation				
Adverse Event	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Protocol Deviation	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Consent Withdrawn	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Lost to Follow-Up	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Death	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Other	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.1.2.1
Demographics – Continuous Variables
PPS Population

		Treatment			
	Statistic	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
Age (years)	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Height (cm)	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Weight (kg)	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
BMI (kg/m^2)	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx

Programming note: table will be created for mITT population: Table 14.1.2.2 Demographics – Continuous Variables, mITT Population

Table 14.1.3.1
Demographics – Categorical Variables
PPS Population

	Treatment			
	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
Ethnicity				
Hispanic/Latino	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Non-Hispanic/Latino	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Race				
White	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
American Indian/Alaska Native	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Asian	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Native Hawaiian or other Pacific Islander	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Black/African American	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Other	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Gender				
Female	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Male	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming note: table will be created for mITT population: Table 14.1.3.2 Demographics – Categorical Variables, mITT Population

Table 14.1.4.1
Prior Medications
PPS Population

ATC Classification	Treatment			
	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming note: table will be created for mITT population: Table 14.1.4.2 Prior Medications, mITT Population

Table 14.1.5.1
Concomitant Medications
PPS Population

ATC Classification	Treatment			
	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
	nn (nn.n%) nn (nn.n%)	nn (nn.n%) nn (nn.n%)	nn (nn.n%) nn (nn.n%)	nn (nn.n%) nn (nn.n%)

Programming note: table will be created for mITT population: Table 14.1.5.2 Concomitant Medications, mITT Population

Table 14.1.6
Dose Administration - Number and Percentage of Patients Who Received IMP by Visit
SAF Population

Visit	Treatment			Overall
	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	N = x
VISIT 2 BASELINE DAY 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 5 WEEK 8	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Etc…

Table 14.1.7
Summary of Dosing Compliance
SAF Population

		Treatment			
	Statistic	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x	Overall N = x
Planned Number of Days IMP exposure	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Actual Number of Capsules used	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
IMP Compliance (%)	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx

The 'actual number of capsules used' was derived as the 'number of capsules dispensed' minus the 'number of capsules returned'.
'Planned number of capsules' is the number of days of per protocol dosing from V2 (first dose) to V8 (last dose), since each patient is to receive 1 capsule of dosing per day of dose administration.
IMP compliance: (actual number of capsules used / planned number of capsules administered) x 100%

Table 14.2.1
NRS Scores Observed and Change from Baseline Summary
mITT Population

Parameter = How Active the target knee arthritis has been

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 5 WEEK 8	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
Etc…							

Programming note: table will include summaries for following other NRS scores:

- Primary endpoint: Amount of pain severity in the target knee last week (SDTM: Overall pain severity in target knee
- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

Table 14.2.2
Number and Percentage of Patients by Category for Duration and Onset of Knee Pain at Baseline
mITT Population

Parameter = Duration of Knee Pain Past 12 Months

	Treatment		
Category	Placebo N = x	100 mg MIV-711 N = x	200 mg MIV-711 N = x
	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Etc…

Programming note: table will include summaries for:

- Duration of Knee Pain Past 12 Months
- Onset of Knee Pain

Table 14.2.3.1
Statistical Analysis Primary Hypothesis - MIV-711 will Reduce Pain in Patients with Moderate Osteoarthritis Assessments Using NRS Scores as Primary Endpoint
mITT Population

Question	Treatment	Week	N	Change From Baseline NRS		Difference From Placebo	
				LS Mean	95% CI	LS Mean Difference	95% CI
	Placebo	8	nn	xx.xx	(x.xx, x.xx)		
		14	nn	xx.xx	(x.xx, x.xx)		
		26	nn	xx.xx	(xx.x, xx.x)		
		30	nn	xx.xx	(x.xx, x.xx)		
NRS question 1: Pain severity in target knee [last week]	100 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)
	200 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:
Low pain scores are associated with a positive outcome (effect of drug).
For positive study expect large (negative changes from week 26) decreases from baseline by the time treatment reaches week 26.

Table 14.2.3.2
Statistical Analysis Primary Hypothesis - MIV-711 will Reduce Pain in Patients with Moderate Osteoarthritis
Assessments Using NRS Scores as Secondary Endpoints
mITT Population

Question	Treatment	Week	N	Change From Baseline NRS		Difference From Placebo	
				LS Mean	95% CI	LS Mean Difference	95% CI
Global Assessment Score: How active was target knee arthritis	Placebo	8	nn	xx.xx	(x.xx, x.xx)		
		14	nn	xx.xx	(x.xx, x.xx)		
		26	nn	xx.xx	(xx.x, xx.x)		
		30	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)
	200 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:
Low pain scores are associated with a positive outcome (effect of drug).
For positive study expect large (negative changes from week 26) decreases from baseline by the time treatment reaches week 26.

Table will be expanded to include the analysis of the following NRS scores:

- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

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Table 14.2.3.3
Statistical Analysis Primary Hypothesis - MIV-711 will Reduce Pain in Patients with Moderate Osteoarthritis Assessments Using NRS Scores as Primary Endpoint
PPS Population

Question	Treatment	Week	N	Change From Baseline NRS		Difference From Placebo	
				LS Mean	95% CI	LS Mean Difference	95% CI
NRS question 1: Pain severity in target knee [last week]	Placebo	8	nn	xx.xx	(x.xx, x.xx)		
		14	nn	xx.xx	(x.xx, x.xx)		
		26	nn	xx.xx	(xx.x, xx.x)		
		30	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)
	200 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:
Low pain scores are associated with a positive outcome (effect of drug).
For positive study expect large (negative changes from week 26) decreases from baseline by the time treatment reaches week 26.

Table 14.2.3.4
Statistical Analysis Primary Hypothesis - MIV-711 will Reduce Pain in Patients with Moderate Osteoarthritis
Assessments Using NRS Scores as Secondary Endpoints
PPS Population

Question	Treatment	Week	N	Change From Baseline NRS		Difference From Placebo	
				LS Mean	95% CI	LS Mean Difference	95% CI
Global Assessment Score: How active was target knee arthritis	Placebo	8	nn	xx.xx	(x.xx, x.xx)		
		14	nn	xx.xx	(x.xx, x.xx)		
		26	nn	xx.xx	(xx.x, xx.x)		
		30	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)
	200 mg MIV-711	8	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		14	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
		26	nn	xx.xx	(xx.x, xx.x)	xx.xx	(x.xx, x.xx)
		30	nn	xx.xx	(x.xx, x.xx)	xx.xx	(xx.x, xx.x)

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:
Low pain scores are associated with a positive outcome (effect of drug).
For positive study expect large (negative changes from week 26) decreases from baseline by the time treatment reaches week 26.

Table will be expanded to include the analysis of the following NRS scores:

- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

Table 14.2.4.1
Imaging variables - MRI of Bone Area for the Target Knee Observed and Change from Baseline Summary
mITT Population

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: source data obtained from MF_TAB: Area of bone in the medial femur region, MF

Table 14.2.4.2
Statistical Analysis - MRI of Bone Area for the Target Knee in Patients with Moderate Osteoarthritis
mITT Population

Question	Treatment	N	Change From Baseline NRS (Visit 8 Week 26)		Difference From Placebo	
			LS Mean	95% CI	LS Mean Difference	95% CI
MRI of Bone Area	Placebo	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
	200 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:

Programming note: source data obtained from MF_TAB: Area of bone in the medial femur region, MF

Table 14.2.4.3
Imaging variables – MRI of Cartilage Thickness for the Target Knee Observed and Change from Baseline Summary
mITT Population

Parameter = *Femur Region*

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: source data obtained from:

- CM_FEMUR_THCTAB: Average thickness of cartilage in the central medial femur region
- CM_TIBIA_THCTAB: Average thickness of cartilage in the central medial tibia region

Table 14.2.4.4
Statistical Analysis - MRI of Cartilage Thickness for the Target Knee in Patients with Moderate Osteoarthritis
mITT Population

Parameter	Treatment	N	Change From Baseline NRS (Visit 8 Week 26)		Difference From Placebo	
			LS Mean	95% CI	LS Mean Difference	95% CI
Femur Region	Placebo	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
	200 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
Etc..						

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:

Programming note: source data obtained from:

- CM_FEMUR_THCTAB: Average thickness of cartilage in the central medial femur region
- CM_TIBIA_THCTAB: Average thickness of cartilage in the central medial tibia region

Table 14.2.4.5
Imaging variables – MRI of Total BML Volume for the Target Knee Observed and Change from Baseline Summary
mITT Population

Parameter = *Femur Region*

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: source data obtained from: TOTAL_BML_VOLUME

Table 14.2.4.6
Statistical Analysis - MRI of Total BML Volume for the Target Knee in Patients with Moderate Osteoarthritis
mITT Population

Parameter	Treatment	N	Change From Baseline NRS (Visit 8 Week 26)		Difference From Placebo	
			LS Mean	95% CI	LS Mean Difference	95% CI
Femur Region	Placebo	nn	xx.xx	(x.xx, x.xx)		
	100 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
	200 mg MIV-711	nn	xx.xx	(x.xx, x.xx)	xx.xx	(x.xx, x.xx)
Etc..						

LS Mean = least squares mean, N denotes the number of Patients for each level of treatment used to estimate the LS means.
Programming notes:

Programming note: source data obtained from: TOTAL_BML_VOLUME

Table 14.2.4.7
Other Imaging variables MOAKS and Imorphics
Number and Percentage of Subjects by Category and Treatment
mITT Population

		Treatment		
		Placebo	100 mg MIV-711	200 mg MIV-711
	Catgeory	N = x	N = x	N = x
Size of BML	None	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	<33%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	33-66%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>66%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Not Evaluable	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Percentage that is BML	None	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	<33%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	33-66%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>66%	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Not Evaluable	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Etc…	Etc…			

Programming note: table will include summaries for the MOAKS and Imorphics imaging variables collected using a categorical response

Table 14.2.4.8
Other Imaging variables MOAKS and Imorphics
Observed and Change from Baseline Summary
mITT Population

Parameter = Number of Bone Marrow Lesions

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: table will include summaries for the other MOAKS and Imorphics variables collected using a quantitative response

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Table 14.2.5
Transformed ICOAP Scores Observed and Change from Baseline Summary
mITT Population

Parameter = Constant Pain

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 5 WEEK 8	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
Etc…							

Programming note: table will include summaries for following transformed ICOAP scores:
Constant Pain, Intermittent Pain, and Total Pain.

Table 14.2.6.1
WOMAC Scores Observed and Change from Baseline Summary - Pain Questions
mITT Population

Parameter = Walking on flat surface

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 5 WEEK 8	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
Etc…							

Programming note: table will be expanded to include all WOMAC Pain questions

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Table 14.2.6.2
WOMAC Scores Observed and Change from Baseline Summary - Stiffness Questions
mITT Population

Parameter = Stiffness after First Woke Up in Morning

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 5 WEEK 8	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
Etc…							

Programming note: table will be expanded to include all WOMAC stiffness questions

Table 14.2.6.3
WOMAC Scores Observed and Change from Baseline Summary - Difficulty Questions
mITT Population

Parameter = Stiffness after First Woke Up in Morning

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 5 WEEK 8	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
Etc…							

Programming note: table will be expanded to include all WOMAC Difficulty questions

Table 14.2.7
Number and Percentage of Patients with a Positive OARSI-OMERACT Response
mITT Population

Parameter = Completely Better

	Treatment		
	Placebo	100 mg MIV-711	200 mg MIV-711
Response	N = x	N = x	N = x
Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.2.8
Number and Percentage of Patients with Each Global Improvement Score Response
mITT Population

Parameter = Knee Problem

Visit	Score	Treatment: Placebo N = x	Treatment: 100 mg MIV-711 N = x	Treatment: 200 mg MIV-711 N = x
VISIT 5 WEEK 8	Completely better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No change	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Completely better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No change	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Completely better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Better	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No change	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Much worse	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming note: table will be expanded to include all Global improvement questions:
Knee Problem, Knee Pain, Ability to use knee.

Table 14.2.9
EQ-5D-5L Health Rating Score Response Observed and Change from Baseline Summary
mITT Population

Parameter = Mobility

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2, Day 1	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: table will be expanded to include all QOL variables:
Mobility, self-care, usual activity, pain or discomfort, and anxiety or depression, health rating score.

Table 14.2.10.1
E-Diary NRS Scores Observed and Change from Baseline Summary, AM Reponse
mITT Population

Parameter = How would you rate overall pain severity over last 12 Hours?

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Table 14.2.10.2
E-Diary NRS Scores Observed and Change from Baseline Summary, PM Reponse
mITT Population

Parameter = How would you rate overall pain severity over last 12 Hours?

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Table 14.2.10.3
E-Diary NRS Scores Observed and Change from Baseline Summary, Overall Response
mITT Population

Parameter = How would you rate overall pain severity over last 12 Hours?

		Treatment					
		Placebo		100 mg MIV-711		200 mg MIV-711	
		Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x
VISIT 2 Baseline	n	nn		nn		nn	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min	xx		xx		xx	
	Max	xx		xx		xx	
VISIT 6 WEEK 14	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx
VISIT 8 WEEK 26	n	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx

Programming note: The mean of the AM, PM NRS scores will be used to obtain 1 record at each visit prior to computing descriptive statistics

Table 14.2.10.4
Number and Percentage of Patients with E-Diary Pain Medication Usage (Yes/No) Over Last 12 Hours, AM Response
mITT Population

Question = Have you taken any pain medication over the last 12 hours since you last answered your OA Daily Diary?

Visit	Score	Treatment: Placebo N = x	Treatment: 100 mg MIV-711 N = x	Treatment: 200 mg MIV-711 N = x
VISIT 2 Baseline	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.2.10.5
Number and Percentage of Patients with E-Diary Pain Medication Usage (Yes/No) Over Last 12 Hours, PM Response
mITT Population

Question = Have you taken any pain medication over the last 12 hours since you last answered your OA Daily Diary?

		Treatment		
Visit		Placebo	100 mg MIV-711	200 mg MIV-711
	Score	N = x	N = x	N = x
VISIT 2 Baseline	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.2.10.6
Number and Percentage of Patients with E-Diary Pain Medication Usage (Yes/No) Over Last 12 Hours, Overall Response
mITT Population

Question = Have you taken any pain medication over the last 12 hours since you last answered your OA Daily Diary?

		Treatment		
Visit		Placebo	100 mg MIV-711	200 mg MIV-711
	Score	N = x	N = x	N = x
VISIT 2 Baseline	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Yes	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	No	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming note: at least one 'Yes' response for AM or PM will be interpreted as a 'Yes' response 24 hours overall.

Table 14.2.10.7
E-Diary Pain Medication Usage Over Last 12 Hours
Number and Percentage of Patients with each Reported Category, AM Response
mITT Population

Visit	Category	Treatment: Placebo N = x	Treatment: 100 mg MIV-711 N = x	Treatment: 200 mg MIV-711 N = x
VISIT 2, Baseline	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.2.10.8
E-Diary Pain Medication Usage Over Last 12 Hours
Number and Percentage of Patients with each Reported Category, PM Response
mITT Population

Visit	Category	Treatment: Placebo N = x	Treatment: 100 mg MIV-711 N = x	Treatment: 200 mg MIV-711 N = x
VISIT 2, Baseline	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 6 WEEK 14	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
VISIT 8 WEEK 26	Less than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	More than Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.3.1.1
Summary of Treatment Emergent Adverse Events
SAF Population

	Treatment			
	Placebo N = x nn (%) E	100 mg MIV-711 N = x nn (%) E	200 mg MIV-711 N = x nn (%) E	Overall N = x nn (%) E
All AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
'Related' AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
Mild AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
Moderate AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
Severe AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
Deaths	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
Serious AEs	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E
AEs Leading to early discontinuation from study	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E	nn (nn.n%) E

TEAE = Treatment Emergent Adverse Event
nn = Number of Patientswith TEAEs
N = Number of PatientsExposed
(nn.n%) = nn/N x 100
E = Number of AEs

Table 14.3.1.2
Number and Percentage of Patients with Treatment Emergent Adverse Events
by System Organ Class, Preferred Term, and Treatment
SAF Population

System Organ Class Preferred Term	Treatment			
	Placebo	100 mg MIV-711	200 mg MIV-711	Overall
	N = x	N = x	N = x	N = x
System Organ Class 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
System Organ Class 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.3.1.3
Number and Percentage of Patients with Treatment Emergent Adverse Events 'Related to IMP'
by System Organ Class, Preferred Term, Severity, and Treatment
SAF Population

System Organ Class Preferred Term	Severity	Treatment			Overall
		Placebo	100 mg MIV-711	200 mg MIV-711	
		N = x	N = x	N = x	N = x
System Organ Class 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
System Organ Class 2	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Etc..					

For patients with multiple adverse events of the same preferred term and different severities, the AE with the highest assessment of severity was used in the summary table.

Table 14.3.1.4
Number and Percentage of Patients with Treatment Emergent Adverse Events 'Not Related to IMP'
by System Organ Class, Preferred Term, Severity, and Treatment
SAF Population

System Organ Class Preferred Term	Severity	Treatment			Overall
		Placebo	100 mg MIV-711	200 mg MIV-711	
		N = x	N = x	N = x	N = x
System Organ Class 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
System Organ Class 2	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	Mild	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Moderate	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Severe	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Etc..					

For patients with multiple adverse events of the same preferred term and different severities, the AE with the highest assessment of severity was used in the summary table.

Table 14.3.1.5
Number and Percentage of Patients with Serious Treatment Emergent Adverse Events
by System Organ Class, Preferred Term, and Treatment
SAF Population

System Organ Class Preferred Term	Treatment			
	Placebo	100 mg MIV-711	200 mg MIV-711	Overall
	N = x	N = x	N = x	N = x
System Organ Class 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
System Organ Class 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.3.1.6
Number and Percentage of Patients with Treatment Emergent Adverse Events Leading to Discontinuation
by System Organ Class, Preferred Term, and Treatment
SAF Population

System Organ Class Preferred Term	Treatment			
	Placebo	100 mg MIV-711	200 mg MIV-711	Overall
	N = x	N = x	N = x	N = x
System Organ Class 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
System Organ Class 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 1	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 2	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term 3	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Preferred Term xx	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Table 14.3.2.1
Clinical Laboratory Chemistry - Summary of Observed Values
SAF Population

Lab Parameter = *Lab Parameter (unit)*

		Treatment			
		Placebo	100 mg MIV-711	200 mg MIV-711	Overall
Visit	Statistic	N = x	N = x	N = x	N = x
Screening	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 2 Baseline Day 1	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 3 Week 2	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 4 Week 4	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Etc…					

Table 14.3.2.2
Clinical Laboratory Hematology - Summary of Observed Values
SAF Population

Lab Parameter = *Lab Parameter (unit)*

		Treatment			
		Placebo	100 mg MIV-711	200 mg MIV-711	Overall
Visit	Statistic	N = x	N = x	N = x	N = x
Screening	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 2 Baseline Day 1	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 3 Week 2	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Visit 4 Week 4	n	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Etc…					

Table 14.3.2.3
Clinical Laboratory Chemistry – Shift From Baseline to Maximum Post-dose Value
SAF Population

Lab Parameter = *Lab Parameter (unit)*

Treatment	Maximum Post-dose Value	Baseline (Visit 2) Low	Normal	High
Placebo	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
100 mg MIV-711	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
200 mg MIV-711	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming Note: Similar table will be created for hematology parameters: Tables 14.3.2.4

Table 14.3.2.5
Clinical Laboratory Chemistry – Shift From Baseline to Minimum Post-dose Value
SAF Population

Lab Parameter = *Lab Parameter (unit)*

Treatment	Maximum Post-dose Value	Baseline (Visit 2) Low	Normal	High
Placebo	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
100 mg MIV-711	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
200 mg MIV-711	Low	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	Normal	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	High	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)

Programming Note: Similar table will be created for hematology parameters: Tables 14.3.2.6

Table 14.3.3
Vital Signs Blood Pressure and Heart Rate Summary of Observed and Change from Baseline Values
SAF Population

Parameter = Systolic Blood Pressure (mmHg)

		Treatment						Overall	
		Placebo		100 mg MIV-711		200 mg MIV-711		N = x	
		Observed	Change	Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x	N = x	N = x
Screening	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Visit 2 Baseline Day 1	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Visit 3 Week 2	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Etc…									

Programming Notes: Table will be expanded to include diastolic blood pressure and heart rate, subject weight

Table 14.3.4.1
12 Lead ECG – Summary of Observed and Change from Baseline Values
SAF Population

Parameter = QT Interval *(unit)*

		Treatment						Overall	
		Placebo		100 mg MIV-711		200 mg MIV-711		N = x	
		Observed	Change	Observed	Change	Observed	Change	Observed	Change
Visit	Statistic	N = x	N = x	N = x	N = x	N = x	N = x	N = x	N = x
Screening	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Visit 2 Baseline Day 1	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Visit 3 Week 2	n	nn	nn	nn	nn	nn	nn	nn	nn
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
Etc…									

QTcB = QT corrected according to Bazett, QTcF = QT corrected according to Fridericia.

Programming note: Table will include: QTcB interval and QTcF interval

Table 14.3.4.2
12 Lead ECG – Categorical Summary of Observed Values
SAF Population

Parameter = QT (msec)

Visit	Category (unit)	Treatment			
		Placebo	100 mg MIV-711	200 mg MIV-711	Overall
		N = x	N = x	N = x	N = x
Screening	≤ 450	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	450 < to ≤ 480	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	480 < to ≤ 500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Visit 2 Baseline Day 1	≤ 450	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	450 < to ≤ 480	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	480 < to ≤ 500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Visit 3 Week 2	≤ 450	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	450 < to ≤ 480	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	480 < to ≤ 500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>500	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Etc…	Etc…				

QTcB = QT corrected according to Bazett, QTcF = QT corrected according to Fridericia.

Programming note: Table will include: QTcB interval and QTcF interval

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Table 14.3.4.3
12 Lead ECG – Categorical Summary of Change from Baseline
SAF Population

Parameter = QT (msec)

Visit	Category (unit)	Treatment			
		Placebo	100 mg MIV-711	200 mg MIV-711	Overall
		N = x	N = x	N = x	N = x
Visit 3 Week 2	<= 0	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>0 to ≤ 30	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>30 to ≤ 60	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>60	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Visit 4 Week 4	<= 0	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>0 to ≤ 30	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>30 to ≤ 60	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
	>60	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)	nn (nn.n%)
Etc…					

QTcB = QT corrected according to Bazett, QTcF = QT corrected according to Fridericia.

Programming note: Table will include: QTcB interval and QTcF interval

15. Listing Shells

Listing 16.2.1.1
Patient Disposition

Treatment = MIV-711 200 mg

Patient	Completion Status	If Discontinued, Day of Withdrawal	If Discontinued, Date of Withdrawal	Reason For Discontinuation	Finalization of Visit 9 (Week 30)	Roll-over to and finalization of Visit 2 of MIV-711-202
	Completed					
	Discontinued					

Listing 16.2.1.2
Patients Excluded from the Analysis Populations

Treatment = MIV-711 200 mg

Patient	Population	Reason for Exclusion
	ITT	
	mITT	
	PPS	
	SAF	

Listing 16.2.1.3
Enrolled Patients Who Did Not Meet All Eligibility Criteria

Treatment = MIV-711 200 mg

Patient	Criteria Category	Criteria Description	Response
	Inclusion		No
	Exclusion		Yes

Listing 16.2.1.4
Exclusion Tests
FSH test, Serology, Urine Drug Screen

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Exclusion Test	Result	Units
				FSH test		
				Etc...		

Listing 16.2.2.1
Protocol Deviations

Treatment = MIV-711 200 mg

Patient	Study Day	Time Point	Date Deviation Occurred	Category	Explanation	Classification
				Time Window		Minor
				Dosing		Major
				Exclusion Tests		Major
				Etc…		

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Listing 16.2.4.1
Demographics

Treatment = MIV-711 200 mg

Patient	Gender	Ethnicity	Race	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)

Listing 16.2.4.2
Medical History

Treatment = MIV-711 200 mg

Patient	Reported Term >MedDRA Preferred Term >>System Organ Class	Onset Date	Status	Recovered Date	Currently Treated with Medication?
			Ongoing		Yes/No

Listing 16.2.5.1
Prior and Concomitant Medications

Treatment = MIV-711 200 mg

Patient	Medication Name >WHO Drug Name >>ATC Classification	Category	Start Date	Stop Date	Ongoing?	Dose/ Unit	Frequency	Route	Indication	Was There an AE	Pain Medication
		Prior CM				Yes/No					Yes/No

Programming note: Pain Medication = 'Yes' if ATC = 'ANALGESICS'

Listing 16.2.5.2
Dose Administration

Treatment = MIV-711 200 mg

Patient	Visit	Date of Dose	Time of Dose	Dose Form / Route	Category of Treatment

Listing 16.2.5.3
Dose Administration Compliance

Treatment = MIV-711 200 mg

Patient	Visit	Date of Dose	Time of Dose	Category of Treatment	Dispensed Amount (Capsules)	Returned Amount (Capsules)	Actual Number of Capsules used	Planned number of capsules	Were all unused Capsules returned?	Reason not all unused Capsules returned	Medication error	Number of Days exposed to IMP	IMP Compliance

The 'actual number of capsules used' was derived as the 'number of capsules dispensed' minus the 'number of capsules returned'.
'Planned number of capsules' is the number of days of per protocol dosing from V2 (first dose) to V8 (last dose), since each patient is to receive 1 capsule of dosing per day of dose administration.
IMP compliance: (actual number of capsules used / planned number of capsules administered) x 100%

Listing 16.2.6.1
Numerical Rating Scale of Knee Pain

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Target Knee Used for NRS	Pain Severity in Target Knee (last week)	Global Assessment NRS	Satisfied with Target Knee Function	Worst Pain Severity Target Knee	Overall pain severity in other knee
	VISIT 2 BASELINE DAY							
	VISIT 5 WEEK 8							
	VISIT 6 WEEK 14							
	Etc…							

Programming note: listing will include:

- Primary endpoint: Amount of pain severity in the target knee last week (SDTM: Overall pain severity in target knee
- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

Listing 16.2.6.2
Numerical Rating Scale of Knee Pain Change From Baseline

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Pain Severity in Target Knee (last week)	Global Assessment NRS	Satisfied with Target Knee Function	Worst Pain Severity Target Knee	Overall pain severity in other knee
	VISIT 2 BASELINE DAY						
	VISIT 5 WEEK 8						
	VISIT 6 WEEK 14						
	Etc…						

Programming note: listing will include:

- Primary endpoint: Amount of pain severity in the target knee last week (SDTM: Overall pain severity in target knee
- Global Assessment Score: How active has the target knee arthritis has been in the past week (SDTM: How active was target knee arthritis)
- Satisfaction with target knee function (SDTM:How satisfied are you with target knee function)
- Worst pain severity in target knee (SDTM: Worst pain severity in target knee)
- Overall pain severity in other knee (SDTM: Overall pain severity in other knee)

Listing 16.2.6.3
Numerical Rating Scale of Knee Pain – Duration and Onset

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Duration of Knee Pain Past 12 Months	Onset of Knee Pain
	VISIT 2 BASELINE DAY			
	VISIT 5 WEEK 8			
	VISIT 6 WEEK 14			
	Etc…			

Listing 16.2.6.4
Imaging Results - MRI of Bone Area for the Target Knee
Observed and Change from Baseline

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	MRI Result - Bone area	MRI - Result - Change from baseline Bone Area
	VISIT 2 BASELINE DAY				
	VISIT 8 WEEK 26				

Programming note: source data obtained from MF_TAB: Area of bone in the medial femur region, MF

Listing 16.2.6.5
Imaging Results - MRI of Cartilage Thickness for the Target Knee
Observed and Change from Baseline

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	Region	MRI Result-Cartilage Thickness	MRI Result - Change from baseline Cartilage Thickness
	VISIT 2 BASELINE DAY					
	VISIT 8 WEEK 26					

Programming note: source data obtained from:

- CM_FEMUR_THCTAB: Average thickness of cartilage in the central medial femur region
- CM_TIBIA_THCTAB: Average thickness of cartilage in the central medial tibia region

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Listing 16.2.6.6
Other Secondary Imaging Variables – MOAKS

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	Question Group Name	Question Sub-Group Name	Question Name	Result Score	Result Score Description	Comments
	VISIT 2 BASELINE DAY VISIT 8 WEEK 26			BML and Cyst	Size of BML	Medial Patella			
						Lateral Patella Medical Femur Trochlea Etc…			
					Number of BMLs	Medial Patella			
						Lateral Patella Medical Femur Trochlea Etc…			
					Percent that is BML	Medial Patella			
						Lateral Patella Medical Femur Trochlea Etc…			
				Cartilage Assessment	Size of Cartilage Loss	Medial Patella			
						Lateral Patella Medical Femur Trochlea			
				Etc…	Etc..	Etc…			

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Listing 16.2.6.7
Other Secondary Imaging Variables Change from Baseline – MOAKS

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	Question Group Name	Question Sub-Group Name	Question Name	Change Score
	VISIT 2 BASELINE DAY VISIT 8 WEEK 26			BML and Cyst	Size of BML	Medial Patella	
						Lateral Patella	
						Medical Femur	
						Trochlea	
						Etc…	
					Number of BMLs	Medial Patella	
						Lateral Patella	
						Medical Femur	
						Trochlea	
						Etc…	
					Percent that is BML	Medial Patella	
						Lateral Patella	
						Medical Femur	
						Trochlea	
						Etc…	
				Cartilage Assessment	Size of Cartilage Loss	Medial Patella	
						Lateral Patella	
						Medical Femur	
						Trochlea	
				Etc…	Etc..	Etc…	

Programming note: only select variables will be considered for change from baseline calculation per sponsor request. Will be noted in final SAP text.

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Listing 16.2.6.8
Other Secondary Imaging Variables – Imorphics

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	Question Group Name	Question Sub-Group Name	Question Name	Result Score	Result Score Description	Comments
	VISIT 2 BASELINE DAY VISIT 8 WEEK 26								

Listing 16.2.6.9
Other Secondary Imaging Variables Change from Baseline – Imorphics
Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	Question Group Name	Question Sub-Group Name	Question Name	Change Score
	VISIT 2 BASELINE DAY VISIT 8 WEEK 26						

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Listing 16.2.6.10
Observed Raw ICOAP Scores

Treatment = MIV-711 200 mg

Patient	Visit	Date of Assessment	Time of Assessment	IP1	IP2	IP3	IP4	IP5	IP6	IP7	IP8	IP9	IP10	IP11
	VISIT 2 BASELINE DAY													
	VISIT 5 WEEK 8													
	VISIT 6 WEEK 14													
	Etc…													

Listing 16.2.6.11
Transformed ICOAP Scores

Treatment = MIV-711 200 mg

				Constant Pain Subscale		Intermittent pain subscale		Total pain score	
Patient	Visit	Date of Assessment	Time of Assessment	Observed	Change	Observed	Change	Observed	Change
	VISIT 2 BASELINE								
	DAY								
	VISIT 5 WEEK 8								
	VISIT 6 WEEK 14								
	Etc…								

Listing 16.2.6.12
Western Ontario and McMaster Index (WOMAC) - Pain Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Walking on a Flat Surface	Going Up or Down Stairs	at Night While in Bed	Sitting or Lying Down	While Standing

Listing 16.2.6.13
Western Ontario and McMaster Index (WOMAC) – Stiffness Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Stiffness after First Woke Up in Morning	Stiffness Sitting or Lying Down

Listing 16.2.6.14
Western Ontario and McMaster Index (WOMAC) - Difficulty Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	When going Down the Stairs	When Going Up the Stairs	Getting Up from a sitting	While Standing	When Bending to the Floor	Walking on a Flat Surface

Programming note: listing will be expanded to show all 17 difficulty questions

Listing 16.2.6.15
Western Ontario and McMaster Index (WOMAC) Change from Baseline – Pain Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Walking on a Flat Surface	Going Up or Down Stairs	at Night While in Bed	Sitting or Lying Down	While Standing

Listing 16.2.6.16
Western Ontario and McMaster Index (WOMAC) Change from Baseline – Stiffness Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Stiffness after First Woke Up in Morning	Stiffness Sitting or Lying Down

Listing 16.2.6.17
Western Ontario and McMaster Index (WOMAC) Change from Baseline – Difficulty Questions

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	When going Down the Stairs	When Going Up the Stairs	Getting Up from a sitting	While Standing	When Bending to the Floor	Walking on a Flat Surface

Programming note: listing will be expanded to show all 17 difficulty questions

Listing 16.2.6.18
OARSI-OMERACT Responder Index
Derived Scores out of 100

Treatment = MIV-711 200 mg

Patient	Visit	Total WOMAC Pain Score [1]	Total WOMAC Function Score [2]	WOMAC Pain Score 100	WOMAC Function Score 100	Global Assessment NRS 100
	Visit 2					
	Visit 8					

[1] Total WOMAC Pain Score (Total_WOMAC_Pain_50): sum of the 5 WOMAC pain responses
[2] Total WOMAC Function Score (Total_WOMAC_Func_170): sum of the 17 WOMAC function responses
Global Assessment NRS = "How Active Target Knee Arthritis Has Been", from Listing 16.2.6.1

WOMAC PAIN Score 100 = Total_WOMAC_Pain_50 x 2.
WOMAC Function Score 100 = Total_WOMAC_Func_170 ÷ 1.7.
Global Assessment NRS 100= (Global Assessment NRS) x 10.

Listing 16.2.6.19
OARSI-OMERACT Responder Index
Change from Baseline and Percentage Change from Baseline Scores

Treatment = MIV-711 200 mg

Patient	Score	Change From Baseline	Percent Change From Baseline	Criteria	Response per Score	Responder
101	WOMAC Pain Score 100	xx	yy		No	No
101	WOMAC Function Score 100	xx	yy		No	
101	Global Assessment NRS 100	xx	yy	5	No	
102	WOMAC Pain Score 100	xx	yy	1	Yes	Yes
102	WOMAC Function Score 100	xx	yy	2	Yes	
102	Global Assessment NRS 100	xx	yy		No	
103	WOMAC Pain Score 100	xx	yy	3	Yes	Yes
103	WOMAC Function Score 100	xx	yy		No	
103	Global Assessment NRS 100	xx	yy	5	Yes	
104	WOMAC Pain Score 100	xx	yy	3	Yes	
104	WOMAC Function Score 100	xx	yy	4	Yes	
104	Global Assessment NRS 100	xx	yy		No	
105	WOMAC Pain Score 100	xx	yy		No	
105	WOMAC Function Score 100	xx	yy	4	No	
105	Global Assessment NRS 100	xx	yy		No	

Percent Change from Baseline: ((Visit 8 Score – Visit 2 Score) ÷ Visit 2 Score) x 100

Criteria 1: WOMAC Pain: decrease from baseline >=20 and **Percentage Decrease from Baseline >=50%**

Criteria 2: WOMAC Function: decrease from baseline >=20 and **Percentage Decrease from Baseline >=50%**

Criteria 3: WOMAC Pain: decrease from baseline >=10 and **Percentage Decrease from Baseline >=20%**

Criteria 4: WOMAC Function: decrease from baseline >=10 and **Percentage Decrease from Baseline >=20%**

Criteria 5: Global Assessment: decrease from baseline >=10 and **Percentage Decrease from Baseline >=20%**

A subject is a 'Yes' responder if either of criteria 1 or 2 are satisfied. If neither criteria 1 or 2 are satisfied, criteria 3, 4 and 5 will be checked. A subject is a 'Yes' responder if at least 2 of these 3 criteria (3, 4, 5) are satisfied.
Programming notes: Criteria column will be flagged with the number 1, 2, 3, 4, 5 only if the conditions for that criteria are satisfied.
Criteria 3, 4, 5 will be shown only if Crteria 1 and 2 have been checked and neither of these intial two conditions are satisfied.

Listing 16.2.6.20
Global Improvements

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Knee problem	Knee Pain	Knee Function

Listing 16.2.6.21
Quality of Life Patient Reported Outcomes - EQ-5D-5L

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Mobility	Self-care	Usual activity	Pain or Discomfort	Anxiety or depression	Health rating score

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Listing 16.2.6.22
Quality of Life Patient Reported Outcomes Change from Baseline Scores - EQ-5D-5L

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Mobility	Self-care	Usual activity	Pain or Discomfort	Anxiety or depression	Health rating score

Listing 16.2.6.23
Brief Medication Questionnaire

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Question	Response
			How much did you take each time	
			How many days did you take it	
			The dosage times are inconvenient	
			Etc…	

Listing 16.2.6.24
E-Diary Assessments over the Last 12 Hours

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Pain medication use over last 12 hours?	Pain medication usage over last 12 hours	NRS: Overall pain severity in target knee over last 12 hours	IMP Intake
			YES	Less than Normal		
			NO	Normal		
				More than normal		

Listing 16.2.6.25
Efficacy Biomarkers from Serum and Urine Samples

Treatment = MIV-711 200 mg

Patient	Visit	Date Of Assessment	Serum CTX-I	urine CTX-II

Listing 16.2.6.26
Time-Integrated Concentrations (TIC) and Their Z-scores
for Efficacy Biomarkers from Serum and Urine Samples

Treatment = MIV-711 200 mg

Patient	Visit	Serum CTX-I	urine CTX-II	Z-Score Serum CTX-I	Z-Score Urine CTX-II

Listing 16.2.7.1
Adverse Events

Treatment = MIV-711 200 mg

Patient	Adverse Event >MedDRA Preferred Term >>System Organ Class	Start Date Time	Stop Date Time	Seri-ous	Outcome	Severity	Action Taken Study Medica-tion [1]	Relation-ship to Study Medica-tion	AE Start Time from First Dose (day)

[1] Action taken results that state 'MEDICATION' indicate a concomitant medication was administered. No action was taken with respect to study medication unless specifically stated otherwise

Listing 16.2.7.2
Serious Adverse Events

Treatment = MIV-711 200 mg

Patient	Adverse Event >MedDRA Preferred Term >>System Organ Class	Start Date Time	Stop Date Time	Outcome	Severity	Action Taken Study Medication [1]	Relationship to Study Medication	AE Start Time from First Dose (day)

[1] Action taken results that state 'MEDICATION' indicate a concomitant medication was administered. No action was taken with respect to study medication unless specifically stated otherwise

Listing 16.2.7.3
Adverse Events Leading To Discontinuation

Treatment = MIV-711 200 mg

Patient	Adverse Event >MedDRA Preferred Term >>System Organ Class	Start Date Time	Stop Date Time	Seri-ous	Outcome	Severity	Action Taken Study Medica-tion [1]	Relation-ship to Study Medica-tion	AE Start Time from First Dose (day)

[1] Action taken results that state 'MEDICATION' indicate a concomitant medication was administered. No action was taken with respect to study medication unless specifically stated otherwise

Listing 16.2.8.1
Clinical Laboratory Chemistry - Observed Values

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Lab Parameter 1 (unit) Result/*Flag*	Lab parameter 2 (unit) Result/*Flag*	Lab parameter 3 (unit) Result/*Flag*	Lab parameter 4 (unit) Result/*Flag*

H=High, L=Low, CS=Clinically Significant, NCS=Not Clinically Significant

Programming Note: If Flag is present (H or L), clinical significance will be identified by one of 'NCS' or 'CS'.

Listing 16.2.8.2
Clinical Laboratory Hematology - Observed Values

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Lab Parameter 1 (unit) Result/*Flag*	Lab parameter 2 (unit) Result/*Flag*	Lab parameter 3 (unit) Result/*Flag*	Lab parameter 4 (unit) Result/*Flag*

H=High, L=Low, CS=Clinically Significant, NCS=Not Clinically Significant

Programming Note: If Flag is present (H or L), clinical significance will be identified by one of 'NCS' or 'CS'.

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Listing 16.2.8.3
Clinical Laboratory Urinalysis - Observed Values

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Lab Parameter 1 (unit) Result/*Flag*	Lab parameter 2 (unit) Result/*Flag*	Lab parameter 3 (unit) Result/*Flag*	Lab parameter 4 (unit) Result/*Flag*

H=High, L=Low, AB=Abnormal, CS=Clinically Significant, NCS=Not Clinically Significant

Programming Note: If Flag is present (H, L, or AB), clinical significance will be identified by one of 'NCS' or 'CS'.

Listing 16.2.8.4
Clinical Laboratory Urinalysis – Positive Microscopic Findings

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Test Name	Result	Unit	Flag	Clinical Significance

*H=High, L=Low, AB=Abnormal, CS=Clinically Significant, NCS=Not Clinically Significant

Programming Note: If Flag is present (H, L, or AB), clinical significance will be identified by one of 'NCS' or 'CS'.

Listing 16.2.8.5
Vital Signs – Observed Values

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Supine Heart Rate (beats/min)	Supine Systolic Blood Pressure (mmHg)	Supine Diastolic Blood Pressure (mmHg)	Pulse Oximetry (%)	Body Temperature (°C)

Listing 16.2.8.6
Vital Signs Change from Baseline

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Supine Heart Rate (beats/min)	Supine Systolic Blood Pressure (mmHg)	Supine Diastolic Blood Pressure (mmHg)

Listing 16.2.8.7
Vital Signs Overall Qualitative Results Abnormal Assessments

Treatment = MIV-711 200 mg

Patient	Visit	Collection Date	Collection Time	Assessment	Interpretation
					ABNORMAL, NCS
					ABNORMAL, CS

NCS = Not Clinically Significant, CS = Clinically Significant

Listing 16.2.8.8
12 Lead ECG Quantitative Findings

Treatment = MIV-711 200 mg

Patient	Visit	Timepoint	Collection Date	Collection Time	Heart Rate (beats/min)	PR (msec)	RR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF (msec)

QTcB = QT corrected according to Bazett, QTcF = QT corrected according to Fridericia.

Listing 16.2.8.9
12 Lead ECG Change From Baseline

Treatment = MIV-711 200 mg

Patient	Visit	Timepoint	Collection Date	Collection Time	QT (msec)	QTcB (msec)	QTcF (msec)

QTcB = QT corrected according to Bazett, QTcF = QT corrected according to Fridericia.

Listing 16.2.8.10
12 Lead ECG Overall Qualitative Assessment

Treatment = MIV-711 200 mg

Patient	Visit	Timepoint	Collection Date	Collection Time	Assess-ment	Interpretation	Comment

NCS = Not Clinically Significant, CS = Clinically Significant

Listing 16.2.8.11
Physical Examination Abnormal Findings

Treatment = MIV-711 200 mg

Patient	Visit	Exam Date	Exam Time	Body System	Abnormality	Clinical Significance
						NCS CS

NCS = Not Clinically Significant, CS = Clinically Significant

Listing 16.2.8.12
Patient Weight

Treatment = MIV-711 200 mg

Patient	Visit	Date	Time	Weight (kg)

Listing 16.2.8.13
Phone Call to Assess Safety

Treatment = MIV-711 200 mg

Patient	Visit	Comments