Official title: A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Single-administration, Multiple-Dose Study to Demonstrate the Efficacy and Safety of MM-II for Treatment of Knee Pain in Subjects With Symptomatic Knee Osteoarthritis

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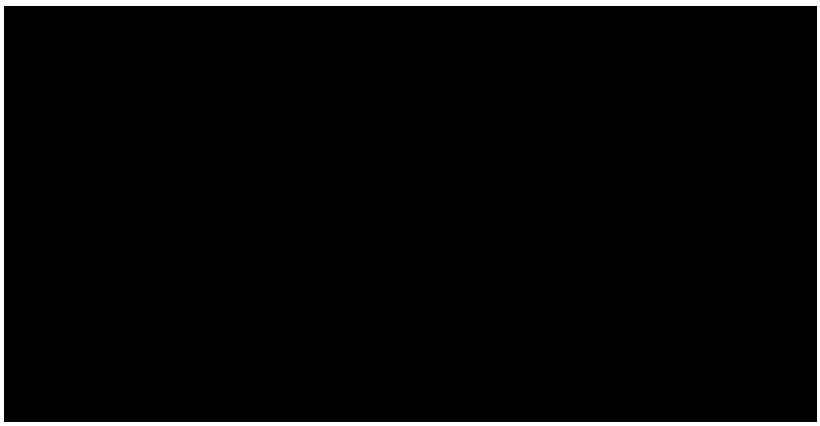

Statistical Analysis Plan

Sponsor:	Sun Pharmaceutical Industries Limited
Protocol No:	CLR_17_17
Protocol Title:	A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Single-administration, Multiple-Dose Study to Demonstrate the Efficacy and Safety of MM-II for Treatment of Knee Pain in Subjects with Symptomatic Knee Osteoarthritis
Document Date:	30-Sep-2022
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
AE	Adverse event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve from time zero to time of last quantifiable concentration
BMI	Body mass index
C_{max}	Maximum observed concentration
COX II	Cyclooxygenase II
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal crosslinking telopeptide of collagen
CV	Coefficient of variation
DMPC	Dimyristoylphosphatidylcholine
DPPC	Dipalmitoylphosphatidylcholine
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End of Study
FAS	Full Analysis Set
huARGS	Aggrecanase degraded aggrecan
IA	Intra-articular
IP	Investigational product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MACE	Major adverse cardiovascular event
MMPs	Matrix metalloproteinases
MMRM	Mixed model repeated measures
NCS	Not clinically significant

Abbreviation	Definition
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PC	phosphatidylcholines
PK	pharmacokinetic
PN	Preferred name
PPAS	Per Protocol Analysis Set
PT	Preferred term
PtGA	Patient Global Assessment
SOC	System organ class
SD	Standard deviation
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum observed concentration
VAS	Visual Analog Scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. INTRODUCTION

1.1 Background

Osteoarthritis (OA) is the most common form of joint diseases, and is characterized by articular cartilage degradation, osteophyte formation, bone remodeling, joint space narrowing, and joint inflammation. It is estimated that 80% of the population will have radiographic evidence of OA by the age of 65 years, although only 20% of those will be symptomatic. The etiology of OA is unknown, but is believed to be multifactorial, including hereditary, metabolic causes, mechanical damages, and inflammatory in nature. Osteoarthritis of the knees has higher prevalence than any other joints. Clinical manifestations of OA in the knees include pain in and around the joint, particularly on weight-bearing of the knee joint, stiffness of the joint after rest, and limited joint motion due to pain and/or stiffness of the joint. The end result of all forms of OA is often loss of function of the joint or limb, imposing significant economic burden on the individuals as well as the society. Diagnosis of OA is based on signs and symptoms, and is often confirmed with imaging studies or using laboratory tests to rule out concomitant inflammatory causes. Since the pathophysiology of OA is unknown, current recommendations for managing OA focus on relieving pain and stiffness, and improving physical function as important goals of therapy. Non-surgical treatment of OA focuses on reducing overloading of joints, physiotherapy, and alleviation of pain and inflammation, usually by topical, systemic, or intra-articular (IA) joint administration of drugs.

Currently available medication regimens for most OA include non-opioid analgesics such as acetaminophen/paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and injectable hyaluronic acid. These pharmaceutical agents can provide transient pain relief quite effectively, but long-term use of NSAIDs has been found to be associated with increased risk of gastrointestinal bleeding, hypertension, cardiovascular events, congestive heart failure, and renal insufficiency, etc. Long-term opioid use for OA is generally discouraged due to lack of information on benefits as well as risks of addiction and other side effects. The NSAIDs in the form of topical application and cyclooxygenase II (COX II) inhibitors are considered somewhat safer than other NSAIDs in terms of gastrointestinal side effects, although COX II inhibitors are contraindicated in patients with a history of coronary artery disease. Because of the high incidence of side effects associated with long-term therapy of both nonselective and COX II selective NSAIDs, effective and safer alternative treatments for OA are urgently needed.

MM-II is composed of two surface active phospholipids [redacted]

[redacted]

1.2 Study Design

This is a randomized, double-blind, placebo-controlled, single administration, multiple-dose, Phase IIb study to evaluate the efficacy of MM-II administered by a single IA joint injection of either MM-II or placebo in subjects with symptomatic knee OA. The study has been developed based on design features used in the completed first-in-human study for the symptomatic knee OA indication. The primary efficacy endpoint is based on the change from Baseline of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A pain score. Secondary efficacy endpoints are based on evaluation of other measures of pain scores, disease activity scores, and weekly cumulative exposure to rescue medication, which are all accepted measures for the evaluation of clinical outcome.

[redacted]

1.3 Rationale

[redacted]

[redacted]

[redacted]

Osteoarthritis of the knees is the most common form of arthritis, both inflammatory and non-inflammatory in nature, particularly after the age of 45. The pathophysiology of OA is poorly understood. Therefore, currently available medication regimens for OA, including non-opioid analgesics such as acetaminophen/paracetamol and NSAIDs, focus on providing transient palliative anti-inflammatory and pain-relieving benefits for OA, as opposed to curative effects. However, long-term use of these agents is associated with a wide range of side effects involving multi-organ systems. Furthermore, these agents have often provided limited and temporary pain relief. Therefore, effective and safer alternative treatments for OA are urgently needed. This Phase IIb, randomized, double-blind, placebo-controlled, single-administration, multiple-dose study is designed to demonstrate the efficacy and safety of MM-II for treatment of knee pain, and to identify an optimal dose in a large population of subjects with symptomatic knee OA. The subjects in the proposed study will receive a single IA joint injection of either MM-II or placebo. Specifically, subjects will be randomized to one of the following treatment arms:

Arm A: MM-II 1 mL IA joint injection,
Arm B: MM-II 3 mL IA joint injection,
Arm C: MM-II 6 mL IA joint injection,
Arm D: Placebo 1 mL IA joint injection,
Arm E: Placebo 3 mL IA joint injection, or
Arm F: Placebo 6 mL IA joint injection.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	**Endpoint(s)**
To determine the optimal dose of an IA joint injection of MM-II in the treatment of knee pain in subjects with symptomatic knee OA	Change from Baseline of WOMAC A pain score at Week 12
Primary Safety Objective	**Endpoint(s)**
To assess the safety and tolerability of a single IA joint injection of MM-II in the treatment of knee pain in subjects with symptomatic knee OA at Week 12	• AEs • Laboratory assessments • Vital signs • ECG • Physical examination

Secondary Objectives	Endpoint(s)
To assess the effect of a single IA joint injection of MM-II in subjects with symptomatic OA	• [redacted] • [redacted] • Change from Baseline in the weekly average of daily knee pain scores by Visual Analog Scale (VAS) at Weeks [redacted] 26[redacted] • Change from Baseline in the weekly average of daily global pain scores by VAS at Weeks [redacted] 26, [redacted] [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. PRIMARY ESTIMAND

Primary Estimand	
Primary scientific question of interest	What is the optimal dose of a single IA joint injection of MM-II as compared to placebo in the treatment of knee pain in subjects with symptomatic knee OA?
Target Population	Defined through appropriate inclusion/exclusion criteria as listed in the study protocol.
Treatments of Interest	• Single IA joint injection of 1 mL MM-II • Single IA joint injection of 3 mL MM-II • Single IA joint injection of 6 mL MM-II
Outcome Variable	Change from Baseline in WOMAC A pain score at Week 12
Summary Measure	Least square mean difference between active doses and 3 mL placebo and associated p-values from a mixed model repeated measures (MMRM) with fixed effects for treatment, visit, and treatment-by-visit interaction and covariates site, Baseline WOMAC A pain score, and randomization stratification factors adjusting for multiplicity using Dunnett's step-down procedure
Intercurrent Events	No adjustments to the primary estimand will be made based on intercurrent events

4. STATISTICAL METHODOLOGY

4.1 General Principles

All collected study data will be presented in listings. All derivations and statistical analyses will be performed using SAS® software Version 9.4. Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced September 1, 2020. Adverse events (AEs) and medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.

Unless stated otherwise, descriptive summaries for continuous variables will include n (number of subjects with non-missing results), mean, standard deviation (SD), median, minimum, and

maximum. For categorical variables, n and percent will be provided. Percentages will be calculated out of the number of subjects in the given population with a non-missing result.

Nominal outcome summaries, presented by collection day and/or by time point, will be based on scheduled assessments as planned in the protocol. Unscheduled assessments will be presented in listings and will not be included in the analyses except for determination of Baseline as described in Section 5.1 and for the derivation of pharmacokinetic parameters. All other visit and time point collections will be as recorded on the electronic case report forms (eCRFs).

The protocol specifies that dosing with study drug will be on Day 0 with study days based on this date. In the context of the SAP and associated tables, figures, and graphs, study days from this point on will be based off of the day of dosing with the day of dosing being Day 1 and the day prior to dosing being Day -1. i.e., there will no Day 0.

Unless otherwise stated, hypothesis testing will be two-sided with an alpha level of 0.05.

4.2 Randomization

Eligible subjects will be randomly assigned to treatment arms A, B, C, D, E, and F in a [redacted] allocation ratio. [redacted]

4.3 Sample Size Considerations

[redacted]

[redacted]

Arm A: MM-II 1 mL IA joint injection [redacted]
Arm B: MM-II 3 mL IA joint injection [redacted]
Arm C: MM-II 6 mL IA joint injection [redacted]
Arm D: Placebo 1 mL IA joint injection [redacted]
Arm E: Placebo 3 mL IA joint injection [redacted]
Arm F: Placebo 6 mL IA joint injection [redacted]

4.4 Sample Size Reassessment

[redacted] After review of the results, the sample size could be kept as originally planned or increased up to 75% to a maximum of 609 subjects with any additional subjects to be randomized using an allocation ratio of [redacted] The blinded sample size reassessment was performed as planned. After reviewing the results, the decision was made not to increase the sample size due to operational reasons.

4.5 Analysis Sets

[redacted] Safety endpoints will be analyzed using the Safety Analysis Set. [redacted]

4.5.1 All Randomized Set

The ARS will include all randomized subjects. Subjects will be analyzed based on their randomized treatment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] **Safety Analysis Set**

The Safety Analysis Set will include all randomized subjects who received the single dose of IP. Analyses will be based on the actual treatment received.

[redacted]

[redacted]

[redacted]

4.6 Subject Disposition

The number of subjects screened and in each of the analysis sets will be summarized by treatment, site, and overall, where applicable.

The number and percentage of subjects who completed the study will be presented by treatment, site, and overall for the All Randomized Set. Frequency and percentage of subjects who withdrew or discontinued from the study, and the primary reason for withdrawal, will also be summarized by treatment and overall.

4.7 Subject Demographics and Baseline Characteristics

Demographic data and subject characteristics at Baseline will be summarized descriptively. These characteristics will include age, sex, reproduction status, contraception method used, ethnicity, race, weight (kg), height (cm), BMI, Rhuematoid Factor, Anti-CCP, Index Knee X-ray, Analgesic

Washout, and all subgroups presented in Section 4.12 by strata. Medical history will be presented by MedDRA system organ class (SOC) and preferred term (PT). Exposure with IP will be summarized by index knee and location of injection.

4.8 Prior and Concomitant Medications

Prior and concomitant medications are classified as follows.

- A prior medication is any medication taken prior to the date of the first dose of study drug.
- A concomitant medication is any medication taken on or after the date of the first dose of study drug.

A medication may be classified as both prior and concomitant. When determining prior or concomitant status for a medication, in the event that the start or end dates of the medication are unknown or incomplete, the medication will be considered as prior and concomitant unless the non-missing date information, if any, is enough to conclude that the medication could not be prior or, separately, could not be concomitant. Incidence of prior and concomitant medication use, according to medications collected on the prior/concomitant medication eCRF page (i.e., excluding rescue medications from the rescue medication dispensing and accountability eCRFs), will be summarized by World Health Organization (WHO) Drug dictionary coded terms Anatomical Therapeutic Chemical (ATC) classification and preferred name (PN).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.9.1 Sensitivity Analysis

Multiple sensitivity analyses will be performed for the change from Baseline in WOMAC A pain score. One will repeat the primary analysis using the PPAS. The primary analysis will also be repeated for the FAS, but pooling the three placebo groups such that treatment in the model has four levels (1 mL, 3 mL, and 6 mL MM-II and pooled placebo). Comparisons of MM-II will be made against pooled placebo for this analysis.

An additional sensitivity analysis will be performed on the change from Baseline in WOMAC A pain score that imputes missing data using multiple imputations (MI) methodology. For the multiple imputations, subjects on MM-II that discontinue due to lack of efficacy will be imputed according to results for subjects randomized to 3 mL placebo. All other missing data will be imputed according to the subject's randomized treatment.

The multiple imputation method will be applied to missing WOMAC A pain scores from Baseline through Week 12 only. The imputation procedure will first begin by generating 100 imputed datasets for subjects that did not discontinue due to lack of efficacy or that were randomized to placebo. The 100 imputed datasets for the WOMAC A pain scores will be generated separately for each randomized treatment with a fully conditional specification (FCS) model using the regression method. The model will include covariates Baseline BMI group (<30 kg/m^2, ≥ 30 kg/m^2 and <35 kg/m^2, ≥ 35 kg/m^2) and Baseline VAS group (≤ 74, ≥ 75). Following these initial imputations, 100 copies of the non-missing WOMAC A pain scores for subjects on MM-II that discontinue due to lack of efficacy will be generated. One of these copies will be added to each of the 100 imputed datasets generated for the 3 mL placebo group. A single imputation will then be generated for each of these 100 combined sets of data using the same FCS model as above. This will result in 100 imputed datasets for all subjects.

Change from Baseline to Week 12 in WOMAC A pain score from each of the 100 imputed datasets will be analyzed separately using an ANCOVA model with effect treatment and covariates site, Baseline WOMAC A pain score, Baseline BMI group (<30 kg/m^2 , ≥ 30 kg/m^2 and <35 kg/m^2, ≥ 35 kg/m^2), and Baseline VAS group (≤ 74, ≥ 75). For each comparison of interest, estimates and their associated standard errors from the ANCOVA models will be combined to produce a single overall

estimate and standard error. Associated two-sided 95% confidence intervals and p-values will then be generated as appropriate.

The SAS® MI procedure will be utilized for imputing data. The first imputation step as described above will be implemented as follows.

```
Proc MI NIMPUTE=100 SEED=1867004294 MINIMUM=. . 0 0 0 0 0
      MAXIMUM=. . 4 4 4 4 4;
  by trt;
  class bmi vas;
  var bmi vas w0 w1 w2 w4 w8 w12;
  fcs reg(w0) reg(w1) reg(w2) reg(w4) reg(w8) reg(w12);
run;
```

Where:
- trt = Treatment (Arms A, B, C, D, E, F)
- bmi = Baseline BMI group
- vas = Baseline VAS group
- w0 = Baseline WOMAC A pain score
- w1 = Week 1 WOMAC A pain score
- w2 = Week 2 WOMAC A pain score
- w4 = Week 4 WOMAC A pain score
- w8 = Week 8 WOMAC A pain score
- w12 = Week 12 WOMAC A pain score

The imputation step for subjects randomized to MM-II that discontinued due to lack of efficacy will be as above except with SEED=454120304, NIMPUTE=1, and without "by trt" since imputation will be based on a single treatment group.

4.10 Secondary Endpoint Analyses

[redacted]

Additionally, change from Baseline in WOMAC A pain score will be analyzed separately at each visit through Week 26 using an ANCOVA model with effect treatment and covariates site,

[redacted]

VAS knee pain and global pain scores are collected daily. Weekly post-baseline average daily scores will calculated for all weeks through Week 26 regardless of whether or not there was a scheduled visit at that week. Weeks will be calculated according to actual study days. Since the Day 1 assessment is scheduled to be collected prior to dosing, Week 1 will be calculated from VAS scores collected on Days 2 through 8, Week 2 from Days 9 through 15, etc. Daily VAS global pain score is only collected prior to dosing on Day 1. Per the definition of baseline in Section 5.1, the last daily VAS global pain score collected prior to the date and time of dosing will be considered baseline for the change from baseline analyses. Daily VAS knee pain score is collected daily leading up to Day 1. Baseline daily VAS knee pain score will be calculated as the average of the assessments on Day 1, if prior to dosing, and the previous six days. Day 1 assessments of average daily knee pain and average daily global pain that are collected after dosing will be excluded from baselin and the Week 1 daily average determination. Weekly averages will be calculated based on the number of days in the week with non-missing pain scores.

The weekly cumulative amount of rescue medication will be based on information from the rescue medication dispensing and accountability eCRF pages only. Weekly cumulative amount of rescue medication will be calculated between each scheduled visit. At each visit, rescue medication is returned and accounted for from the previous visit and new rescue medication is dispensed. It will be assumed that no rescue medication was taken on the day of return unless rescue medication was also dispensed on that date. If so, then the dosage taken for that day will be based on the accountability for the newly dispensed rescue medication. The amount of rescue medication taken between visits will be based on the "number of tablets consumed" and the associated "dosage per tablet" as captured on the eCRFs. For a given period (dispensing through return), the average daily dose of rescue medication will be calculated. It will be assumed that the subject consumed this average daily dose of rescue medication on each date in the period. Dates for which a subject is in the study, but do not fall within one of the dispensing and return periods or the date of return where no new rescue medication was dispensed, will be assumed to have no rescue medication received. The days associated with a given visit include the date of the previous visit through the day prior to the current visit. Weekly cumulative amount of rescue medication for a given visit will be calculated by summing up the daily doses within the period, dividing by the number of days in the period, and then multiplying by seven. Subjects with missing information for a given period will have their weekly cumulative amount of rescue medication set to missing for that period. Subjects discontinuing early will be analyzed in the MMRM analysis only through the last scheduled visit. However, rescue medication usage after this visit through the date of early termination will be summarized under the heading "Last Visit". Subjects completing the study

that have a calculable Week 26 weekly cumulative amount of rescue medication will have their Week 26 results summarized under Week 26 and "Last Visit".

[redacted]

[redacted]

4.12 Subgroup Analysis

The primary endpoint and WOMAC C disability sub-scores will be analyzed using separate mixed model repeated measures for the following subgroups:

- Baseline WOMAC A pain score (≤ median, > median)
- BMI (<30 kg/m^2, ≥ 30 kg/m^2 and < 35 kg/m^2, and ≥ 35 kg/m^2)
- Baseline Index Knee Pain (VAS: ≤74, ≥75)

The median for the Baseline WOMAC A pain score will be calculated based on the FAS.

Change from Baseline to Week 12 in WOMAC A pain score will be summarized descriptively for the following groups:

- Age (≤ 65 years, > 65 years)
- Sex (Male, Female)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Site
- Region (US Sites, Denmark Sites, Hong Kong Site)

4.13 Plasma Concentration and Pharmacokinetic Analyses

Plasma DMPC and DPPC concentration data will be listed by individual subject and summarized by time and MM-II dose group. PK parameters of AUC, C_{max}, C_{min}, and T_{max} will be summarized with descriptive statistics (n, mean, SD, geometric mean, coefficient of variation (CV), minimum, first, second (i.e., median) and third quartiles, and maximum). The PK Analysis Set will be used for the analysis. PK analysis will only be conducted at US sites.

AUC will be determined from the linear trapezoidal method using non-compartmental analysis. Pre-dose concentrations will be analyzed at time 0. All other concentrations will be analyzed using their actual time post-dose. Concentrations below the lower limit of quantification (LLOQ)

occurring before the first quantifiable concentration will be analyzed as 0. Concentrations below the LLOQ occurring after the first quantifiable concentration will be considered missing. If a quantifiable concentration during the elimination phase occurs after an elimination phase concentration that is below the LLOQ, the concentration will be examined to determine if the concentration should be included in the calculation.

4.14 Safety Analyses

Safety will be assessed by adverse events, laboratory assessments, vital sign measurements, ECG data, index knee examination, and physical examination abnormalities using the Safety Analysis Set.

4.14.1 Adverse Events

An AE is defined as "any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of an investigation product, whether or not related to the investigational product".

Any relevant observations made (including physical examination findings, clinically relevant abnormal vital signs, clinically relevant laboratory abnormalities, and clinically relevant ECG findings) prior to or after administration of the single dose of IP are to be recorded on the AE eCRF. An AE relating to a pre-existing condition will only be recorded if there is a worsening of the pre-existing condition during study conduct with regard to nature, severity or frequency. An event will be considered a treatment-emergent AE (TEAE) if the start or worsening of the event was on or after the administration of IP. Summaries of adverse events will be limited to TEAEs, but listings of all events will be provided. A serious adverse event is an event recorded as 'Serious' on the adverse event eCRF page. Adverse events will be classified by MedDRA SOC and PT.

The overall summary of TEAEs will include frequencies and percentages and will be presented for the following:

- Overview of adverse events;
- All adverse events by SOC and PT;
- Serious adverse events SOC and PT;
- Adverse events by SOC, PT, and severity;
- Adverse events related to study treatment by SOC and PT

An adverse event will be considered related to study drug if the relationship is "possibly", "probably", or "certainly". The severity of an adverse event will be rated by the investigator as "mild", "moderate", or "severe". Subjects experiencing multiple instances of the same PT are only counted once within each SOC and PT combination. Subjects experiencing multiple instances of the same PT will only be counted once according to the highest severity during the treatment emergent period when summarizing severity.

Serious adverse events, if present, also will be listed using verbatim and SOC/PT. Should any serious adverse events occur during the study, the serious adverse events are displayed in a table and a narrative for each serious adverse event included in the study report.

Adverse Events of Special Interest (AESIs) will be summarized descriptively. AESI-related safety endpoints include:

- Percent of subjects with severe infections, defined as any infection meeting the regulatory definition of a SAE, or any infection requiring IV antibiotics whether or not reported as a serious event, as per the regulatory definition
- Percent of subjects with malignancies (excluding carcinoma in situ of the cervix)
- Percent of subjects with non-melanoma skin cancer
- Percent of subjects with melanoma skin cancer
- Percent of subjects with major adverse cardiovascular event (MACE)
- Percent of subjects with treatment-related hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, etc.)

All AEs will be presented in full in a comprehensive listing including subject number, treatment regimen, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop and duration. Details of SAEs and AEs leading to withdrawal will be listed separately.

4.14.2 Vital Signs Measurements

Vital sign observed values and changes and shifts from Baseline will be summarized at each scheduled visit, where applicable. Shifts will be presented for parameters that are further classified as "Normal", "Abnormal Not Clinically Significant (NCS)" and "Abnormal Clinically Significant (CS)". Abnormal NCS and Abnormal CS will be combined and displayed as "Abnormal" in the shift tables. A listing of all clinically significant abnormal results will be presented.

4.14.3 Clinical Laboratory Tests

Clinical laboratory parameters (e.g., albumin, etc.), including observed values and changes and shifts from Baseline, will be summarized at each scheduled visit, where applicable. Laboratory

parameters may be classified as "Low", "Normal", or "High" (quantitative parameters) or "Abnormal" or "Normal" (qualitative parameters) by the central laboratory according to the reference ranges provided in the laboratory data transfer. "Low", "High", and "Abnormal" results will be flagged in the listings of individual subject data. Some parameters may not have normal ranges.

Urine drug, urine cotinine, urine alcohol, FSH, serology, coagulation, and pregnancy test results will also be presented in data listings.

4.14.4 ECGs

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with "Normal", "Abnormal, not clinically significant", and "Abnormal, clinically significant". Shifts from Baseline in overall ECG interpretation will also be presented for "Normal" and "Abnormal". A listing of all clinically significant abnormal overall ECG interpretations will be presented. Continuous ECG parameter (e.g., QTcF) observed values and changes from Baseline will be summarized per schedule.

4.14.5 Physical Examinations

Physical examination results will be summarized with incidence of "Normal", "Abnormal NCS" and "Abnormal CS" by body system at each scheduled visit. Shifts from Baseline will also be presented by body system for "Normal" and "Abnormal". A listing of all clinically significant abnormal results will be presented.

5. DATA HANDLING

5.1 Baseline, Pre-Dose, and Study Visits

Baseline daily VAS knee pain score will be calculated as the average of the assessments on Day 1 and the previous six days. For all other parameters, the last non-missing value, including unscheduled, of a variable taken before the single dose of IP will be used as the Baseline value. Except for determination of the PK parameters, all post-Baseline unscheduled data will be excluded from the analyses and presented in the listings only. Except for pharmacokinetic concentration data used to derive PK parameters, which will be analyzed at the actual sampling times, including unscheduled, all other analyses presented by collection day and/or by time point will be based on the schedule of assessments as planned in the protocol and recorded on the eCRFs. However, subjects who prematurely discontinue from the study having their final visit assessments collected on the Week 26 eCRFs. For these subjects, data collected under Week 26 will be mapped to one of the scheduled visits based on the following visit windows. On a per data point basis, if no scheduled result exists for the mapped visit, then the Week 26 will be used in the analysis for

that visit. If there is a scheduled result associated with the mapped visit, then the original scheduled result for that visit will be used in the analysis and the mapped Week 26 result will be presented in the listings only.

Visit	Target Study Day	Study Day Range
Week 1[a]	8	1 – 11
Week 2	15	12 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127
Week 20	141	128 – 162
Week 26	183	≥ 163
a: Day 2 assessments are scheduled for specific hours on that day. Any subject discontinuing prior to Week 1 will have their early termination assessments mapped to Week 1 and not to specific hours on Day 2 regardless of the date.		

5.2 Pooling of Sites

Sites contributing less than 16 subjects to the PPAS will be pooled within region (US Sites, Denmark Sites, Hong Kong Site). Pooling will begin by sorting the sites within a region based on the number of subjects in the PPAS. The site with the lowest number of subjects will be pooled with the site with the next lowest number of subjects. If necessary, pooling with subsequent sites will continue until the pooled site contains at least 16 subjects in the PPAS. Pooling for additional sites will continue until all sites/pooled sites within a region have at least 16 subjects in the PPAS. Pooled site will be used for all analyses (e.g., MMRM) containing site in the model or site as a stratification factor. If a site does not have any subjects in the PPAS, then it will be combined with the pooled site containing the greatest number of individual sites within the same region. If there is more than one pooled site with the greatest number of individual sites, then it will be combined with the pooled site with the fewest number of total subjects.

5.3 Missing Data

WOMAC A pain scores will be imputed as described in Section 4.9.1 for the sensitivity analysis based on multiple imputations. All other analyses will based on available data. Handling of plasma values that are BQL with respect to the pharmacokinetic analyses are described in Section 4.13.

5.4 Unscheduled Data

Unscheduled PK collections will be used for the derivation of the PK parameters. For all other data obtained from unscheduled assessments, results will only be considered for Baseline determination; otherwise, unscheduled data will not be used in summary tables or included in the analyses. All unscheduled data will be presented in the listings.

5.5 Presentation Conventions

For all parameters, where applicable:

- n: no decimal place,
- CV% and CV% geometric mean will be displayed to one decimal place,

For the following pharmacokinetic parameters, where applicable:

- Arithmetic mean, geometric mean, SD, median, minimum, and maximum:
  - t_{max}: two decimal places,
  - C_{max} and AUC,: four significant figures.

All other parameters that are reported or derived at a fixed number of decimal points (e.g., vital sign measurements, including body mass index (BMI), clinical laboratory test parameters, and plasma drug concentrations), will be reported as follows:

- Mean, median, and first and third quartiles will be displayed to one more decimal than the maximum number of decimal places reported for the original data,
- SD will be reported to two more decimal places than the maximum number of decimal places reported for the original data,
- Minimum and maximum will be reported to the maximum number of decimal places reported for the original data.

5.5.1 Significant Figures

When descriptive statistics are to be presented to a specific number of significant figures, the following conventions will be utilized:

- Results of "0" will be displayed as "0".
- Results that cannot be displayed to the exact specified number of significant figures (in Section 3.5) without the use of scientific notation will be displayed using the maximum number of significant figures that is less than the specified number of significant figures.

E.g., "1000" and "1295" cannot be displayed to three significant figures without the use of scientific notation, so "1000" and "1300" would be presented, respectively.

- All other results will be displayed to the specified number of significant figures in Section 3.5. Examples of results displayed to three significant figures are presented below:

Original Result	Presentation Result (3 Significant Figures)
12.34	12.3
0.01234	0.0123
0.12	0.120
10	10.0
1234	1230

6. DEVIATIONS FROM THE PROTOCOL

The protocol specifies that the primary endpoint analysis will be performed by first testing for an overall treatment effect prior to testing pairwise comparisons using Fisher's LSD Test. Comparisons between MM-II doses and 3 mL placebo will instead be analyzed using a step-down Dunnett testing method.

The wording of the subgroup analysis was clarified from the protocol as the subgroups themselves are not covariates but rather ways to separately analyze different subsets of the total subject population of interest.

The summary of physical examinations was changed to include Abnormal CS and Abnormal NCS to better reflect the information provided by the eCRF.

The protocol specified summarizing treatment compliance but was deemed unnecessary since this is a single injection study.

The reference to "confirmed" when discussing MACE was removed since MACE events will not be adjudicated.

The definition of the FAS in the protocol required subjects to have at least one post-Baseline primary efficacy assessment. The definition of the FAS has been modified to no longer require subjects to have at least one post-Baseline primary efficacy assessment.

The definition of the PPAS was modifed to require a non-missing Week 12 primary efficacy assessment instead of any non-missing post-baseline assessment and to exclude subjects with other factors that could influence the validity of the data for the primary efficacy variable that are not major protocol deviations.