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

Document: Clinical Study Protocol

NCT number: NCT04506463

Document date: 18 Jun 2021

CLINICAL STUDY PROTOCOL

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

Protocol No.:	CLR_17_17
Test Product:	MM-II (large liposomes of DMPC & DPPC)
Indication:	Treatment of Knee Pain in Subjects with Symptomatic Knee Osteoarthritis
Sponsor:	Sun Pharmaceutical Industries Limited. Sun House, Plot No 201 B/1, Western Express Highway, Goregaon (E) - 400063, Mumbai, Maharashtra, India.
Development Phase:	Phase IIb
Sponsor Signatory:	[redacted] 2 Independence Way Princeton, NJ 08540
Sponsor Medical Expert:	[redacted] 2 Independence Way Princeton, NJ 08540
Initial protocol, A0 - date:	18 Aug 2020
Amendment no. - date:	2 – 18 Jun 2021

1 SIGNATURE PAGES

1.1 SPONSOR SIGNATURE PAGE

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

PROTOCOL NUMBER: CLR_17_17

SPONSOR: Sun Pharmaceutical industries Ltd. (SPIL)

[redacted]

1.2 General Information

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

Protocol No.:	CLR_17_17
[redacted]	[redacted]
Sponsor:	Sun Pharmaceutical Industries Ltd. Sun House, Plot No 201 B/1, Western Express Highway, Goregaon (E) - 400063, Mumbai, Maharashtra, India.
[redacted]	[redacted]
Pharmacokinetics:	Pharmacokinetics Department Sun Pharmaceutical Industries Ltd., Tandalja, [redacted]

[redacted]

2 STUDY SYNOPSIS

Name of Sponsor/Company: Sun Pharmaceutical Industries Ltd	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: MM-II [redacted]		
[redacted]	**Volume:** **Page:**	

Title of Study:
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 (OA)

Study Centers:
The study will be multinational and multicenter.

Publication(s):
None.

Planned Study Period:	**Development Phase:**
2020 – 2022	Phase IIb

Objectives:

Primary Efficacy Objective:

- To determine the optimal dose of a single intra-articular (IA) joint injection of MM-II in the treatment of knee pain in subjects with symptomatic knee OA as measured by the change from Baseline of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A pain score at Week 12.

Primary Safety Objective:

- 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.

Secondary Objectives:

- To assess the effect of a single IA joint injection of MM-II in subjects with symptomatic knee OA as measured by the change from Baseline for:
  - WOMAC A pain score at Week 26 and over time
  - WOMAC stiffness and disability sub-scores at Weeks 12, 26 and over time
  - The weekly average of daily index knee pain scores by visual analog scale (VAS) at Weeks 12, 26 and over time
  - The weekly average of daily global pain scores by VAS at Weeks 12, 26 and over time
  - Patient Global Assessment (PtGA) of disease activity at Weeks 12, 26 and over time
- To assess the effect of a single IA joint injection of MM-II in subjects with symptomatic OA as compared to placebo at Weeks 12, 26 and over time as measured by the weekly cumulative amount of rescue medication (only acetaminophen/paracetamol allowed)

- 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 26 and over time, excluding Week 12,

[redacted]

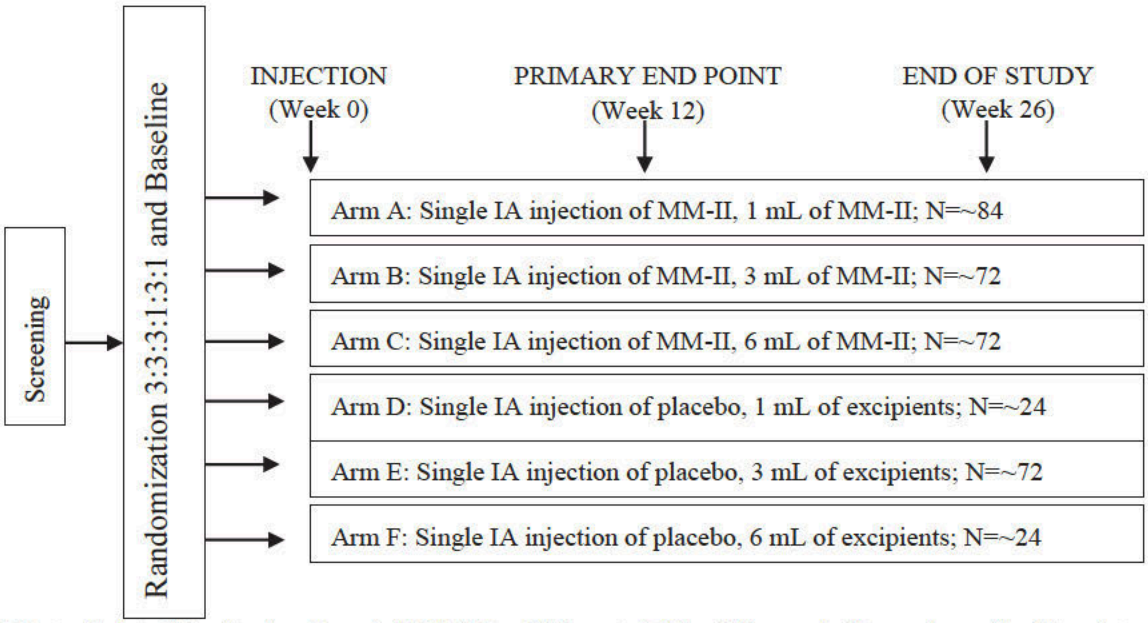
Methodology:

This is a 27-week, phase IIb, randomized, double-blind, placebo-controlled, single-administration, multiple-dose study to determine the efficacy and safety of a single IA joint injection of MM-II in subjects with symptomatic knee OA as compared to matching placebo. The primary endpoint will be change in WOMAC A pain score (See Appendix 18.2) from Baseline at Week 12, [redacted]

The duration of participation is up to 27 weeks. Subjects will be screened for eligibility during a period of up to 28 days, followed by randomization and a single IA knee joint injection on Day 0 (Week 0) and then a 26-week follow-up period. Subjects may voluntarily withdraw from participation in the trial at any time.

Approximately 348 subjects with knee pain due to symptomatic OA of the knee who have met the inclusion criteria will be randomized [redacted] The primary efficacy endpoint is the change from Baseline in WOMAC A pain score at Week 12. Secondary efficacy endpoints will include change from Baseline in WOMAC A pain score at Week 26, WOMAC stiffness and disability sub-scores at different time points, weekly average of daily index knee pain scores and weekly average of daily global pain by VAS at Weeks 12 and 26, PtGA of disease activity, the weekly cumulative amount of rescue medication (acetaminophen/paracetamol) used.

[redacted]



A Data Safety Monitoring Board (DSMB) will be established for periodic review of safety data for this study.

Number of Subjects:

It is planned that approximately 348 subjects will be randomized to the treatment.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects may be included in the study if they meet all of the following criteria:

1. Subject is able to provide written consent, understand study requirements, is prepared to complete study procedures and is able to independently communicate meaningfully with study personnel.
2. Men or women ≥ 40 years of age at the time of Screening.
3. Radiographic evidence of knee OA [redacted]

5. Presence of index knee pain for at least 6 months prior to Screening.

[redacted]

[redacted]

Exclusion Criteria:

Subjects should be excluded from the study if they meet any of the following criteria:

1. Presence of moderate to severe pain in any other joints, including non-index knee, spine, or the rest of the body in most of the days (meaning more than half) within 7 days prior to Screening
2. Concomitant moderate or large size synovial fluid effusion of the index knee at Screening or Baseline.
3. Known diagnosis of infection in the index knee in the past five years prior to Screening.

[redacted]

[redacted]

[redacted]

21. Subjects with a history of alcohol or drug abuse in the previous 2 years.

[redacted]

25. Female subjects of childbearing potential who do not agree to practice established effective methods of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential must ensure that their female partners use highly effective birth control as described above and a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy). Contraceptive methods must be practiced for the entire study duration. If a subject discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of IP. A follicle stimulating hormone (FSH) test should be performed to confirm menopause for those women with no menses for less than 1 year.
26. Female is pregnant or breast feeding, or planning to become pregnant or initiate breastfeeding while enrolled in the study.
27. Subject will not be available for protocol-required study visits, to the best of the subject's and Investigator's knowledge.
28. Subject previously has been randomized in this study or has previous received treatment with MM-II.
29. Donation or loss of 400 mL or more of blood within 12 weeks before dosing.
30. Subjects who have been placed in an institution on official or judicial orders.
31. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.
32. Have a condition or be in a situation which, in the investigator's opinion, may put the subject at a significant risk, may confound study results, or may interfere significantly with the subject's participation in the study. This criterion provides an opportunity for the investigator to exclude subject based on clinical judgment, even if other eligibility criteria are satisfied.

Reference Therapy, Dose and Duration of Administration:

[redacted]

Concomitant Medications, Supportive Care, and Study Restrictions:

Concomitant medications limited throughout the study:

- Acetaminophen/paracetamol may be used by the subject (no more than 4 gram daily) as needed for index knee breakthrough pain [redacted]

Duration of Treatment:

A total of 27 weeks.

Variables:

Efficacy:

Primary Endpoint:

The change from Baseline of WOMAC A pain score at Week 12 to identify an optimal dose of MM-II.

Secondary Endpoints:

- The secondary efficacy endpoints are the change from Baseline for:
  - WOMAC A pain score at Week 26 and over time [redacted]
  - The weekly average of daily knee pain scores by VAS at Weeks [redacted] 26 [redacted]
  - The weekly average of daily global pain scores by VAS at Weeks [redacted] 26 [redacted]

[redacted]

[redacted] ours (day 7) after IP injection with a sampling window of +/- 60 minutes from the time of IP-injection.

Pharmacodynamics:

Safety: The following information will be collected for assessment of safety:

- AEs
- Laboratory assessments
- Vital signs
- Electrocardiogram
- Physical examination
- The weekly cumulative amount of rescue medication

Statistical Methods:

Sample Size: ~ 348

Approximately 348 subjects will be randomized following screening in this study. The randomization allocation ratio would be [redacted] initially. [redacted] he randomization will be centralized over all sites.

Approximately 348 subjects are expected to result in the approximate following subjects' allocations:
[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]

With approximately 72 evaluable subjects per arm for the primary endpoint (Arms A, B, C, and E), the study is powered at 80% with an alpha level of 0.05 assuming a baseline WOMAC A (0-4; mean of 5 questions) pain score of 2.0 with standard deviation of 0.59 and a change from Baseline in the WOMAC A pain score of 0.52 (26%) and 0.8 (40%) for placebo and MM-II, respectively, yielding a difference of 0.28 between the groups.

For primary efficacy endpoint will be analysed with Mixed Effect Model (MMRM) with fixed effects for treatment group, study visit, treatment-by-visit interaction, site and baseline covariates. Subject will be included as random effect. Treatment differences will be estimated for all Active Arms (A, B, C) vs Placebo 3 mL arm (E) will be estimated via least square means from the analysis model along with 95% confidence intervals, and associated 2-sided p-values

The study will begin with the sample size yielding at least 80% power under an optimistic scenario assuming SD = 0.59. After 80% of the study subjects are enrolled, the assumptions for SD will be re-

checked in blinded fashion, and the sample size could be increased. The sample will not be increased more than a maximal total of N=609. If increase in the sample size is required post blinded sample size re-estimation, enrolment of the additional patients after accrual of 348 patients would be done using an allocation ratio of 3:3:3:1:3:1. Enrolment for the study will then continue until the new target sample size is reached. The enrolment size at each site will be capped at no more than 20% of the overall sample size.

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Anti-CCP Ab	Anti-cyclic citrullinated peptide antibodies
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
COX II	Cyclooxygenase-II
CP	Conditional power
CRO	Contract research organization
CTX	C-terminal crosslinking telopeptide of collagen
DMPC	Dimyristoylphosphatidylcholine
DPPC	Dipalmitoylphosphatidylcholine
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EoS	End of Study
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HbA1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
huARGS	Aggrecanase degraded aggrecan
IA	Intra-articular
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee

INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ISC	Independent statistical center
IXRS	Interactive voice/web response system
LTBI	Latent tuberculosis infection
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMPs	Matrix metalloproteinases
MLVs	Multilamellar vesicles
NOAEL	No-observed-adverse-effect-level
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PA	Posterior-anterior
PC	Phosphatidylcholines
PD	Pharmacodynamics
PFS	Pre-filled syringe
PGA	Physician global assessment
PI	Principal investigator
PK	Pharmacokinetic
PN	Preferred name
PPAS	Per protocol analysis set
PRN	As needed (pro re nata)
PT	Prothrombin time
PtGA	Patient global assessment
QTcF	Qtc corrected according to the Fridericia formula
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIB	Suicidal ideation and behavior
$T_{1/2}$	Half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

T_{max}	Time of maximal concentration
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells
WHO	World health organization
WOMAC	Western Ontario and McMaster universities osteoarthritis index
β-hCG	Beta human chorionic gonadotropin

3 INTRODUCTION

3.1 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[1,2]. The etiology of OA is unknown, but is believed to be multifactorial, including hereditary, metabolic causes, mechanical damages, and inflammatory in nature[2,3]. Osteoarthritis of the knees has higher prevalence than any other joints[1,3]. 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[1–3]. 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[1,2].

Currently available medication regimens for most OA include non-opioid analgesics such as acetaminophen/paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and injectable hyaluronic acid[1,2,4]. 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[1,2,4]. 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]

3.2 Discussion of 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 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]

3.3 Rationale

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3.1 Rationale for Dose

In the completed first-in-man single-center, exploratory study, MM-II has demonstrated efficacy and safety comparable to a hyaluronic acid active-comparator. [redacted]

This Phase IIb dose ranging study will evaluate the previously tested 3 mL dose, as well as doses [redacted]

[redacted]

[redacted]

3.3.2 Rationale for Study

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 either MM-II (1 mL, 3 mL, or 6 mL) or placebo (1 mL, 3 mL, or 6 mL) in a single IA joint injection of the knee.

3.3.3 Risk/Benefit and Ethical Assessment

Given that efficacy benefits were reported for subjects with concurrent OA in the completed first- in-human study in symptomatic knee OA, there is an expectation that MM-II will improve OA knee pain and measures of quality of life in a larger OA subject population at Week 12. Furthermore, rescue medication is allowed for additional pain control during the study for subjects who experience breakthrough knee pain caused by knee OA.

The study has also been designed to minimize potential risks to subjects; all subjects will undergo screening procedures aimed at reducing the likelihood and impact of any such risks, for example, subjects on anticoagulation or have a history of coagulopathy are excluded from this study due to a need for IA knee injection. In addition, regular safety monitoring during the evaluation period for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately.

An independent Data Safety Monitoring Board (DSMB) will review selected data across the study. The DSMB in conjunction with the Sponsor is empowered to make recommendations regarding continuation, termination or modification of the study, as appropriate.

Overall, based on data from non-clinical and clinical studies of MM-II to date and the risk minimization strategies discussed above, the risk: benefit profile of the current study is considered acceptable.

3.3.4 Statistical Justification

Statistical analysis for the primary endpoint will be based on comparison of the change from baseline between the treatment groups. The comparison will be done by longitudinal mixed effect model (MMRM) with fixed effects for treatment group, study visit, treatment-by-visit interaction, site and baseline covariates. [redacted]

[redacted]

Approximately 348 subjects are expected to result in the approximate following subjects' allocations:

[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] or

[Arm F] placebo 6 mL IA joint injection [redacted]

[redacted] With approximately [redacted] evaluable subjects per arm for the primary endpoint [redacted] the study provides 80% power with an alpha of 0.05. [redacted]

4 STUDY OBJECTIVES

4.1 Primary Efficacy Objective

- 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 as measured by the change from Baseline of WOMAC A pain score at Week 12.

Hypothesis: MM-II at an optimal dose is superior to placebo in the treatment of knee pain caused by symptomatic knee OA as measured by improvement in the WOMAC A pain score from Baseline to Week 12.

4.2 Primary Safety Objective

- 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.

MM-II treated subjects are expected to show fewer or equal moderate to severe adverse events (AEs) as compared to placebo.

4.3 Secondary Objectives

- To assess the effect of a single IA joint injection of MM-II in subjects with symptomatic OA as measured by the change from Baseline for:
  - WOMAC A pain score at Week 26 and over time
  - [redacted]
  - The weekly average of daily knee pain scores by Visual Analog Scale (VAS) at Weeks [redacted] 26 [redacted]
  - The weekly average of daily global pain scores by VAS at Weeks [redacted] 26 and [redacted]
  - [redacted]

[redacted]

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

5.1.1 Description

This is a 27-week, phase IIb, randomized, double-blind, placebo-controlled single-administration, multiple-dose study to evaluate the efficacy and safety of a single IA joint injection of MM-II in subjects with symptomatic knee OA who have failed to respond adequately to simple analgesics as compared to matching placebo. The design of the study is illustrated in Figure 5-1 below. The study will be multinational and performed in a number of study centers. Screening of subjects for eligibility will take place during a period of up to 28 days, followed by randomization and a single IA joint injection of the index knee on Day 0 (Week 0) and then a 26-week follow-up period. [redacted] Approximately 348 subjects with symptomatic knee OA will be randomized to receive a single IA injection of MM-II or placebo into the index knee at a volume of 1 mL, 3 mL, or 6 mL in this study. [redacted] n the Standard Protocol for IA Injection. The subject is blinded for the duration of the study.

The primary endpoint is the change from Baseline in WOMAC A pain score (See Appendix 18.2) at Week 12. Secondary efficacy endpoints will include change from Baseline WOMAC A score at Week 26, WOMAC stiffness and disability sub-scores at Weeks 12, 26, and over time, knee joint pain by VAS at measured time points, global pain score by VAS at measured time points, the weekly cumulative amount of rescue medication (acetaminophen/paracetamol) used, and PtGA of disease activity.

[redacted]

[redacted]

[redacted]

A DSMB will be established for periodic review of safety data for this study.

This study will be conducted in compliance with the protocol and with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP).

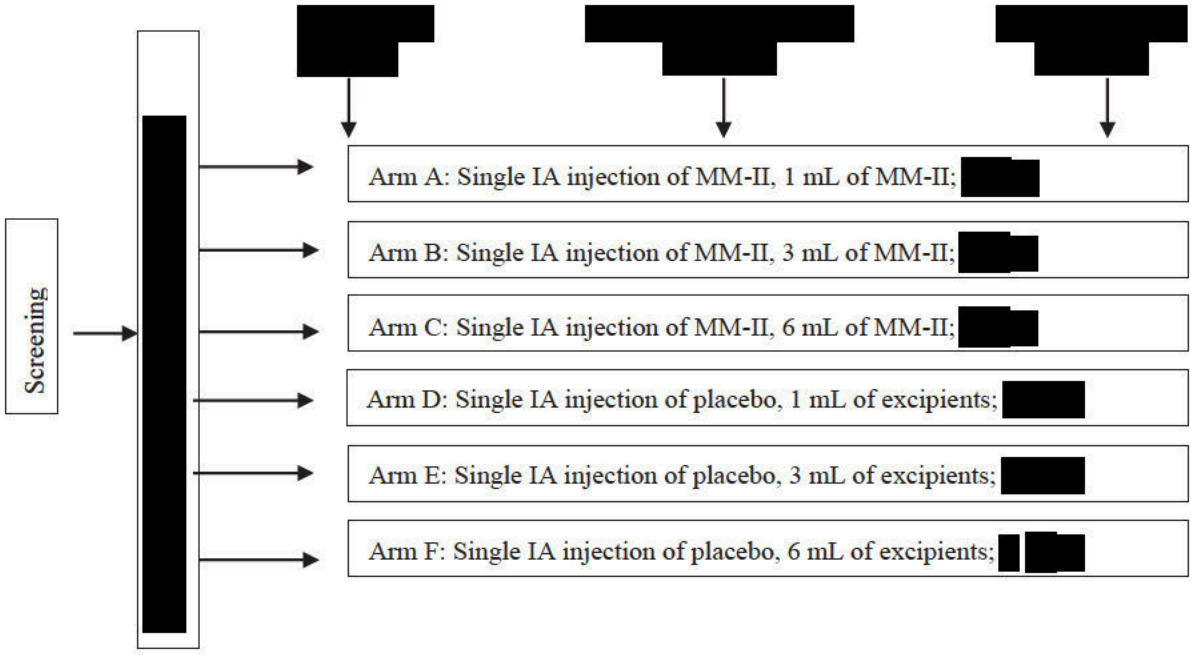


Figure 5-1 Study Design - Randomization Groups

5.1.2 Adaptive Increase in Sample Size

[redacted]

5.1.3 Study Assessments

The schedule of study assessments is presented in Table 5-1 and details of the study procedures are provided in Sections 5.1.4, 7, and 8. The Sponsor or designee and CRO will be notified immediately of any critical deviation from study procedures. All protocol deviations will be routinely examined by the Sponsor or designee and CRO.

The study will consist of a Screening Period and Baseline assessments, followed by the Active Treatment, and Follow-up Period:

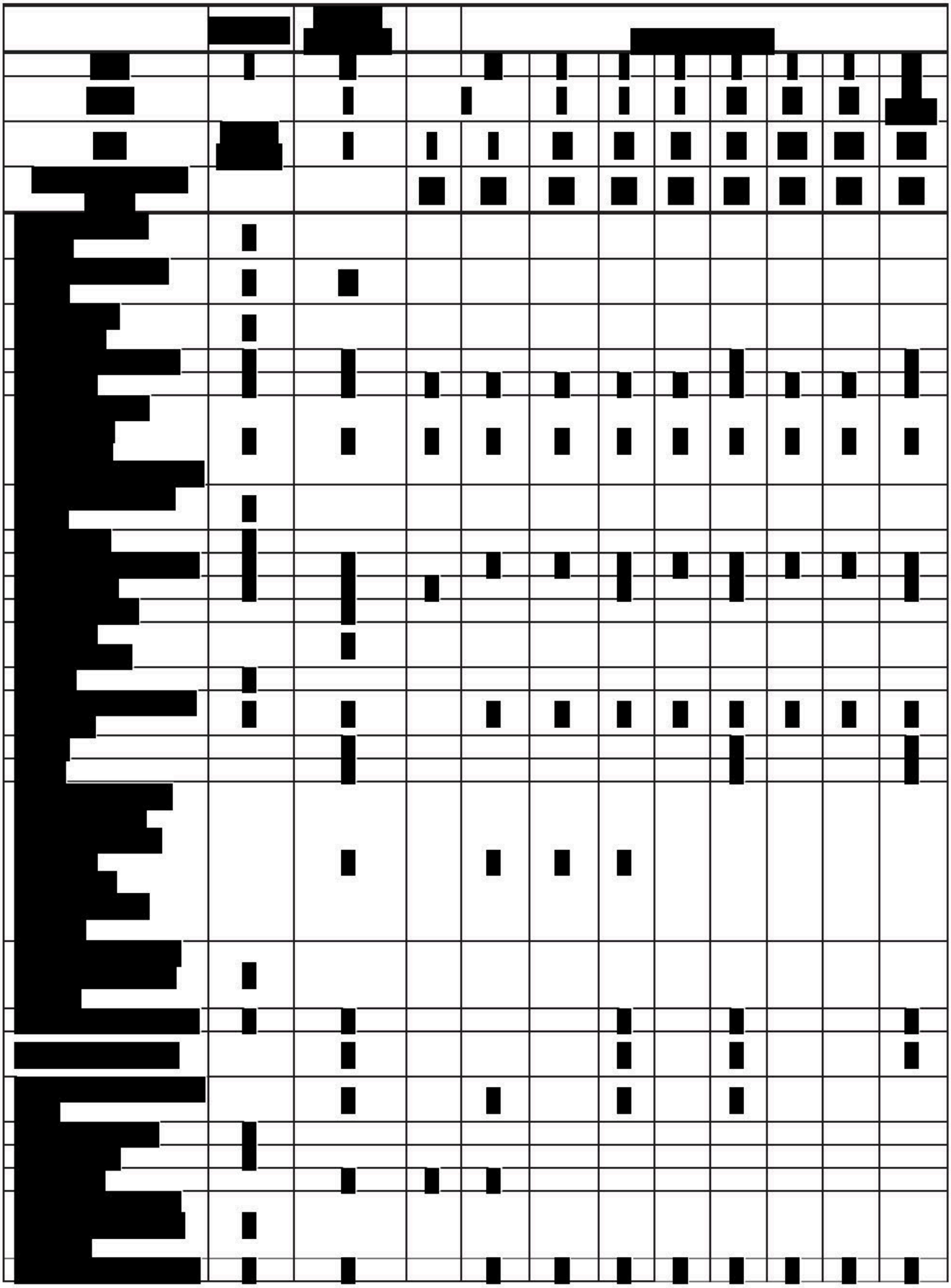
- Screening (Day -28 to Day 0), followed by Baseline assessments and randomization,
- Active Treatment: Double-blind, placebo-controlled period (Day 0, Week 0),
- Follow-up Period (Day 0, Week 0 to Week 26), starting immediately after the IP administration.

[redacted]

[redacted]

5.1.4 Schedule of Assessments

The Schedule of Assessments is presented in Table 5-1.



[redacted]

[redacted]

[redacted]

[redacted]

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Subject is able to provide written consent, understand study requirements, is prepared to complete study procedures and is able to independently communicate meaningfully with study personnel.
2. Men or women ⩾40 years of age at the time of Screening.
3. Radiographic evidence of knee OA [redacted]
5. Presence of index knee pain for at least 6 months prior to Screening.

[redacted]

5.2.2 Exclusion Criteria

Subjects should be excluded from the study if they meet any of the following criteria:

1. Presence of moderate to severe pain in any other joints, including non-index knee, spine, or the rest of the body in most of the days (meaning more than half) within 7 days prior to Screening.

2. Concomitant moderate or large size synovial fluid effusion of the index knee at Screening or Baseline.
3. Known diagnosis of infection in the index knee in the past five years prior to Screening.

[redacted]

[redacted]

21. Subjects with a history of alcohol or drug abuse in the previous 2 years.

[redacted]

- [redacted]
- [redacted]

25. Female subjects of childbearing potential who do not agree to practice established effective methods of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential must ensure that their female partners use highly effective birth control as described above and a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy). Contraceptive methods must be practiced for the entire study duration. If a subject discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of IP. A follicle stimulating hormone (FSH) test should be performed to confirm menopause for those women with no menses for less than 1 year.
26. Female is pregnant or breast feeding, or planning to become pregnant or initiate breastfeeding while enrolled in the study.
27. Subject will not be available for protocol-required study visits, to the best of the subject's and Investigator's knowledge.
28. Subject previously has been randomized in this study or has previous received treatment with MM-II.
29. Donation or loss of 400 mL or more of blood within 12 weeks before dosing.
30. Subjects who have been placed in an institution on official or judicial orders.
31. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.
32. Have a condition or be in a situation which, in the investigator's opinion, may put the subject at a significant risk, may confound study results, or may interfere significantly with the subject's participation in the study. This criterion provides an opportunity for the investigator to exclude subject based on clinical judgment, even if other eligibility criteria are satisfied

5.2.3 Strategies for Subject Recruitment and Retention

All recruitment material will be approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to implementation.

Regular study monitoring will enable identification of any potential issues related to subject retention.

5.2.4 Withdrawal of Subjects

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. A subject may withdraw from the study at any time without giving any reason; and should a subject be removed from the study or elect to decline further study participation, the Sponsor will be notified and the reason(s) for discontinuing the study will be recorded in the source documents and eCRF.

[redacted]

5.2.5

5.2.8 Replacement of subjects

Subjects who drop out after randomization will not be replaced.

5.2.9 Premature discontinuation of the complete study

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

[redacted]

6 TREATMENT OF SUBJECTS

6.1 Investigational product

6.1.1 Study Products:

MM-II: Each vial of IP contains 3 mL of MM-II aliquoted into a vial. [redacted]

Placebo: Each vial of placebo will be presented in identical containers as MM-II [redacted]

6.1.2 Dosing and Dosage Regimen

Subjects will receive a single IA joint injection of MM-II or matched placebo [redacted]

The following arms will be included:

- Arm A: Single IA joint injection of MM-II (1 mL of MM-II) [redacted]
- Arm B: Single IA joint injection of MM-II (3 mL of MM-II) [redacted]
- Arm C: Single IA joint injection of MM-II (6 mL of MM-II) [redacted]
- Arm D: Single IA joint injection of placebo (1 mL of excipients) [redacted]
- Arm E: Single IA joint injection of placebo (3 mL of excipients) [redacted]
- Arm F: Single IA joint injection of placebo (6 mL of excipients) [redacted]

[redacted]

6.1.3.2 Labeling

Treatment labels will comply with the legal requirements of each country and be printed in the local language as applicable. Treatment labels will not contain any information about the subjects.

[redacted]

[redacted]

6.1.4 Investigational Product Numbering

Each IP will be uniquely numbered. The study product number(s) will be recorded in the source documents.

6.1.5 Accountability Procedures for the Investigational Product

The Sponsor will supply sufficient quantities of the study product to allow completion of this study, in an appropriate package deemed to maintain the integrity of the products. In accordance with GCP, the study site will account for all supplies of study product. The supplies will be stored per label instructions until dispensed, in a pharmacy accessible only to pharmacist or authorized person. Details of receipt, storage, assembly, dispensing, and return will be recorded.

[redacted]

[redacted]

[redacted]

6.3 Procedures for Monitoring Subject Compliance

The dosage, timing and mode of administration of study treatment may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

[redacted]

6.3.1 Blinding and Randomization of Study Treatment(s)

[redacted]

[redacted]

Should a situation arise where unblinding is required, the Investigator at that site may perform immediate unblinding via the IWRS with or without following an attempt for communication with the Sponsor depending on local legislature. This can only occur in emergency situations (Section 6.4).

[redacted]

6.4 Procedure for Breaking the Randomization Code

Subjects, Investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until all subjects complete their double-blind follow-up (Week 26 visit) and the study database has been cleaned and locked.

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, knowledge of the possible treatment assignments is sufficient to treat a study subject who presents with an emergency condition. Emergency code breaks are performed using the IWRS. The detailed procedure of emergency code breaking and unblinding the subject is described in the eCRF/IWRS completion guideline available to study site and staff prior to study start.

[redacted]

7 ASSESSMENT OF EFFICACY

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments (Table 5-1).

7.1 Efficacy Assessments

[redacted]

[redacted]

[redacted]

.

7.1.2 WOMAC Evaluation of Knee Osteoarthritis

The current WOMAC survey is comprised of 24 items divided into three subscales: Pain (5 items), stiffness (2 items), and physical function (17 items). Subjects are asked a range of questions about their knee pain, knee stiffness, their ability to carry out daily activities such as using the stairs, rising from sitting, lying in bed and conducting light or heavy domestic duties. All the items are scored on a scale of 0-4 (lower scores indicate lower levels of symptoms or physical disability). Values are summed up for a combined WOMAC score (WOMAC total score) or subscores (WOMAC A pain score, etc), and means can be calculated for total and subscores on the 0-4 scale. This is a common method used, although other aggregation methods have been used. The higher the score, the higher the amount of pain, stiffness, and a high level of functional limitations.

7.1.3 Weekly Average of Daily Knee Pain by VAS

The subjects will be asked a question: "By tapping on the line, please indicate how much knee pain on average you have had in your <L/R> knee during the past 24 hours." The subjects will respond to the questions on a VAS scale (0 – 100), the lower on the scale, the less the amount of knee pain experienced.

7.1.4 Weekly Average of Daily Global Pain Scores by VAS

The subjects will be asked a question: "By tapping on the line, please indicate how much overall pain on average you have had during the past 24 hours." The subjects will respond to the questions on a VAS scale (0 – 100), the lower on the scale, the less the amount of global pain experienced.

7.1.5 Patient Global Assessment of Disease Activity

The subject will assess their current global status of symptomatic knee OA by means of a VAS ("Considering all the ways your knee osteoarthritis affects you, please indicate by tapping on the line, on average, how have you been doing during the last 24 hours?").

8 ASSESSMENT OF SAFETY

8.1 Safety Endpoints

The following safety parameters will be assessed during the study as per the Table 8-1 and are described below:

8.1.1 Laboratory Assessments

Laboratory measurements for blood chemistry, hematology and urinalysis will be performed [redacted]

8.1.2 Clinical Laboratory Tests

Unless otherwise indicated, all chemistry and hematology parameters will be analyzed using a central laboratory. [redacted]

8.1.3 Electrocardiogram Assessments

Computerized 12-lead ECG recordings will be obtained at scheduled study visits after the subject has rested for at least 5 minutes in the supine position. [redacted]

8.1.4 Physical Examination

A standard complete physical examination will be performed at [redacted]

8.1.5 Vital Signs

Body temperature, systolic and diastolic cuff blood pressure (measured after at least 5 minutes in the supine position) and pulse rate (measured after at least 5 minutes in the supine position) [redacted]

[redacted]

8.1.6 Pregnancy testing

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening visit. A[redacted]

Pregnancies must be reported to the CRO within 24 hours of awareness.

8.2 Definitions

8.2.1 Adverse Event/Reaction

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".

[redacted]

An adverse treatment reaction is an "untoward and unintended response to an IP related to any dose administered". All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an IP qualify as adverse treatment reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments which suggest a causal relationship.

8.2.2 Serious Adverse Event

A SAE is any untoward medical occurrence that, at any dose

- results in death
- is life-threatening
- requires in-subject hospitalization or prolongation of existing hospitalization*
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.), convulsions that do not result in hospitalization, or the development of treatment dependency or treatment abuse.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

*A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social / logistic reason) are not to be considered as SAEs.

8.2.3 Suspected Unexpected Serious Adverse Reactions and Unexpected Adverse Reactions

Any suspected adverse reaction that is serious, unexpected, and considered to be related to treatment exposure is defined as a suspected unexpected serious adverse reaction (SUSAR).

An unexpected AE is any adverse treatment event, which is not listed in the current IB or is not listed at the specificity or intensity that has been observed.

An untoward and unintended post dosing response to a non-study treatment is, by definition, not a SUSAR, but is, however, an AE.

8.2.4 Overdose

A treatment overdose is defined as the accidental or intentional use of a treatment or an administration error in an amount that is higher than is normally used. Every overdose must be reported to designated CRO within 24 hours of awareness, irrespective of whether the overdose was associated with an AE/SAE.

[redacted]

8.2.6 Abnormal laboratory values/vital signs/electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as AEs/SAEs if it is clinically significant and any of the following criteria is met:

- Result is associated with signs/symptoms
- Requires additional diagnostic testing and/or intervention

Any test result determined to be an error or simple repetition of a laboratory test is not required to be reported as an AE.

8.2.7 Anaphylaxis

The clinical criteria for diagnosing anaphylaxis are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING* a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours): a) Involvement of the skin-mucosal tissue (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence) d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure *to <u>known</u> allergen for that patient* (minutes to several hours): a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow

Data source: Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.

8.3 Causality of AEs

The following system will be used by the Investigator (Global Introspection assessment) as a guiding tool to assess treatment relationship: Unrelated, unlikely, possibly, probably and certainly.

TERM	DEFINITION	CLARIFICATION
Unrelated	Those AEs which, after careful consideration, are clearly due to extraneous causes (medical history, demography details, disease, environment, *etc.*)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other treatments, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the treatment. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant treatments or chemicals including food-treatment interactions

Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other treatments or chemicals. Information on treatment withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from administration of the treatment. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant treatments or chemicals (including food-treatment interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the treatment.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other treatments or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.	1. It follows a reasonable temporal sequence from administration of the treatment. 2. It could not be readily explained (unlikely) by the patient's concurrent disease, environmental factors, medical history and other concomitant treatments or chemicals including food-treatment interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the treatment, yet treatment relatedness clearly exists. 4. No rechallenge information is available or possible.
Certainly	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to treatment administration, and which cannot be explained by concurrent disease or other treatments or chemicals. The response to withdrawal of the treatment (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	1. It follows a plausible time sequence to treatment intake, this means that there is a positive argument in sufficient detail to support the view that the treatment is causally involved, pharmacologically or pathologically e.g. pharmacokinetics and type of reaction. 2. It could not be explained by patient's concurrent disease, environmental factors, medical history and other concomitant treatments or chemicals including food-treatment interactions (i.e. no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a treatment that had been given previously. *This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation).* 5. It reappears on readministration of the treatment (only if ethically correct i.e. in case of non-serious, and easily treatable AEs).

Assessments of Unlikely and Unrelated do not meet the threshold for reasonable suspected causal relationship and are therefore classified as Unrelated for regulatory reporting and within a binary scale of Related/Not Related.

The Investigator should consider the following before reaching a decision on causality assessment:

- Time relationship between IP use and event's onset
- Medical history
- Study treatment
- Mechanism of action of IP
- Class effect
- Concomitant treatments in use
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study treatment or concomitant medication
- Protocol-related process

8.4 Assessment of severity, outcome and expectedness of Adverse Events

The severity of an AE will be characterized as:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE, which prevents normal daily activities.
- Life-threatening: The subject is at risk of death due to the AE as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.
- Death: Death related to AE

Event outcome is categorized as: fatal, resolved, resolved with sequelae, resolving, not resolved, or unknown.

Action taken with respect to study treatment due to an AE is categorized as: none, unknown, or not applicable.

Other actions taken are categorized as: none, specific therapy/medication, surgical medical procedure, or (Prolonged) hospitalization.

Assessment of Expectedness will be determined by the version of the IB effective at the time of onset of the adverse event

8.5 Eliciting, Documentation and Reporting of Adverse Events

Information on AEs will be derived by questioning the subjects in general terms (e.g. "How do you feel?" or "How have you been feeling since the last questioning?" respectively), by subjects' spontaneous reports, or by observation.

AEs will be documented on the source document. Trained monitors will check the entries on the source document. The AE will be transcribed to the AE eCRF-sections. The following information will be given for each AE: Description of the AE, start date, stop date, severity,

pattern, action taken, outcome, seriousness, dose of study treatment, and relationship to the study treatments. The dose of study treatment assigned to an AE will be the dose the subject was assigned to take on the date the subject reported the AE first began.

8.6 Reporting of Serious Adverse Events, Adverse Events of Special Interest

All SAEs must be reported according to ICH guidelines on GCP or local regulations, applying the regulation with the stricter requirements.

[redacted]

All AEs/SAEs will be recorded on the AE Report Form in the eCRF and source documents. The Investigator is responsible for informing the IEC or IRB of the SAE as per local requirements.

SAE forms should be completed at the site and faxed/emailed to the relevant Sponsor / designated CRO or emailed to the global email distribution list within 24 hours of awareness of the event. The Investigator is responsible for informing the IEC or IRB of the SAE as per local requirements.

SAE and AESI reports should be sent to:

Central Receipt mail box: [redacted]

If the report is sent via email then the completed and signed SAE or Pregnancy Report Form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

There may be situations when an SAE (or AESI) has occurred and the Investigator has minimal information to include in the initial SAE report. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE Report Form. Minimum criteria are identifiable subject (number), a suspect product (i.e., IP or concomitant medication), an identifiable reporting source (Investigator/study site identification), and an event or outcome that can be identified as serious. The Investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE report form accordingly. The causality assessment is the criteria used when determining regulatory reporting requirements for SAEs.

8.6.1.1 Safety Reporting to Sponsor

Designated CRO will forward the SAE and Pregnancy report to the following Sponsor's safety representatives within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

[redacted]

8.6.1.2 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

Designated CRO will notify the Sponsor or designee of any SAE and will perform follow-up activities with the concerned site. The Sponsor will bear responsibility of expedited and periodic reporting to the Health Authorities according to national requirements.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) to the IEC/IRB that approved the study. Investigators should provide written documentation of IEC/IRB notification for each report to the Designated CRO.

In accordance with ICH GCP, Designated CRO will inform the Investigators of findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular and in line with respective regulations, Designated CRO will inform the Investigators of SAEs. The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

8.7 24/7 Medical Emergency Coverage

In a study-related emergency situation occurring outside of usual business hours, when site Investigators cannot be reached by a caller, assigned Medical Monitors, followed by an on-call physician can be reached 24 hours per day, 7 days per week.

[redacted]

[redacted]

[redacted]

[redacted]

Any [redacted]

[redacted]

[redacted]

9 STATISTICAL EVALUATION

9.1 Study Arms Description

The study will have six (6) arms, denoted by Arm A to Arm F. The former three arms are active and will receive a single injection of MM-II by an IA joint injection [redacted] at a volume of 1 mL, 3 mL, or 6 mL. The latter three arms are Placebo and subjects will receive a single injection of Placebo injection into the [redacted] at a volume of 1 mL, 3 mL, or 6 mL. [redacted]

In summary:

- Arm A: Single IA joint injection of MM-II (1 mL of MM-II) [redacted]
- Arm B: Single IA joint injection of MM-II (3 mL of MM-II) [redacted]
- Arm C: Single IA joint injection of MM-II (6 mL of MM-II) [redacted]
- Arm D: Single IA joint injection of placebo (1 mL of excipients) [redacted]
- Arm E: Single IA joint injection of placebo (3 mL of excipients) [redacted]
- Arm F: Single IA joint injection of placebo (6 mL of excipients) [redacted]

9.2 Randomization

A randomization schedule will be computer-generated before the start of the study. [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.

9.5.4 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects in the [redacted]

9.6 Endpoints

[redacted]

9.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The change from Baseline in the WOMAC A pain score at Week 12.

9.6.3 Secondary Efficacy Endpoints (up to Week 26)

The secondary efficacy endpoints are as follows:

- To assess the effect of a single IA joint injection of MM-II in subjects with symptomatic OA as measured by the change from Baseline for:

- [redacted]
- [redacted]
- The weekly average of daily knee pain scores by VAS at Weeks [redacted] 26 [redacted]
- The weekly average of daily global pain scores by VAS at Weeks [redacted] 26 [redacted]

[redacted]

These parameters will be assessed using the PK Analysis Set.

9.7 Description of Statistical Analyses

9.7.1 General Statistical Methods

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, SD, median, and range will be provided. For categorical variables, the number and percentage in each category will be displayed.

Assessments of change from Baseline to post-Baseline will include only those subjects with both Baseline and post-Baseline measurements. The last value of a variable taken before the single dose of IP will be used as the Baseline value. Unless otherwise specified, missing or dropout data will not be imputed for the purpose of data analysis.

A more detailed description of study analyses will be presented in the SAP that will be finalized before the sample size reassessment.

9.7.2 Analysis of Primary Endpoint

[redacted]

[redacted]

[redacted]

Physical Examination

[redacted]

10 DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Conduct of the Study

Sponsor and CRO shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures and study manuals to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP R2 and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013)[10], Food and Drug Administration (FDA) (CFR, Sections 312.50 and 312.56), EU (Annex 1, Directive 2001/83/EC) and UK regulations (The Medicines for Human Use [Clinical Trials] Regulations 2004 [no.1031]), and with ICH GCP R2 (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

11.2 Study Monitoring

The Investigator shall permit the Sponsor/designated CRO Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator will provide access medical records for the monitor in order that entries in the eCRF may be verified. The Investigator, as part of his/her responsibilities, is expected to co-operate with Sponsor/designated CRO in ensuring that the study adheres to GCP requirements.

12 ETHICS

12.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments, written informed consent forms and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

12.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The process of obtaining informed consent must be documented in the subject source documents.

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with FDA, ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

[redacted]

[redacted]

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms/Source Data Handling

All required study data must be entered in the eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based EDC software system. The Investigator shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded. All internal Sponsor/designated CRO and external investigational site personnel seeking access to the eCRF are supported by the CRO data manager. At the end of the study all data captured electronically will be provided to the Investigator for archiving at the investigational site.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory, unless otherwise specified (e.g., ESR).

The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the subject's file.

13.2 Retention of Essential Documents

The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

14 FINANCING AND INSURANCE

The Sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the Sponsor will cover the cost. The Sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, the Sponsor may refuse or restrict the payment of the compensation:

1. A serious GCP or protocol deviation by the Investigator or Sub-Investigator (except deviation medically necessary to avoid an immediate hazard to the study subjects)
2. Intentional act or negligence on the part of the Investigator or Sub-Investigator or malpractice thereby
3. Injury caused by unlawful act or delinquency of a third party
4. Injury caused by intentional act or negligence of the subject

If compensation becomes necessary for a study-related injury, the site will promptly notify the Sponsor and will co-operate with the Sponsor and its insurer (or their legal representatives) in their handling thereof.

15 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 REFERENCE LIST

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18 APPENDIX

18.1 SYNOPSIS OF AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR OSTEOARTHRITIS

(https://www.rheumatology.org/Portals/0/Files/Idiopathic%20OA%20of%20the%20Knee.pdf)

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain	Knee pain	Knee pain
+at least 5 of 9	+at least 1 of 3	+at least 3 of 6
-Age >50 years	-Age >50 years	-Age >50 years
-Stiffness <30 min	-Stiffness <30 min	-Stiffness <30 min
-Crepitus	-Crepitus	-Crepitus
-Bony tenderness	+Osteophytes	-Bony tenderness
-Bony enlargement		-Bony enlargement
-No palpable warmth		-No palpable warmth
-ESR <40 mm/hour		

18.2 WOMAC SCALE

PATIENT NAME | DOB

WESTERN ONTARIO AND
MCMASTER OSTEOARTHRITIS INDEX (WOMAC)
Please circle the appropriate rating for each item.

RATE YOUR PAIN WHEN...	NONE	SLIGHT	MODERATE	SEVERE	EXTREME	HOSPITAL USE ONLY
Walking	0	1	2	3	4	
Climbing stairs	0	1	2	3	4	
Sleeping at night	0	1	2	3	4	
Resting	0	1	2	3	4	
Standing	0	1	2	3	4	TOTAL
RATE YOUR STIFFNESS IN THE...	**NONE**	**SLIGHT**	**MODERATE**	**SEVERE**	**EXTREME**	**HOSPITAL USE ONLY**
Morning	0	1	2	3	4	
Evening	0	1	2	3	4	TOTAL
RATE YOUR DIFFICULTY WHEN...	**NONE**	**SLIGHT**	**MODERATE**	**SEVERE**	**EXTREME**	**HOSPITAL USE ONLY**
Descending stairs	0	1	2	3	4	
Ascending stairs	0	1	2	3	4	
Rising from sitting	0	1	2	3	4	
Standing	0	1	2	3	4	
Bending to floor	0	1	2	3	4	
Walking on even floor	0	1	2	3	4	
Getting in/out of car	0	1	2	3	4	
Going shopping	0	1	2	3	4	
Putting on socks	0	1	2	3	4	
Rising from bed	0	1	2	3	4	
Taking off socks	0	1	2	3	4	
Lying in bed	0	1	2	3	4	
Getting in/out of bath	0	1	2	3	4	
Sitting	0	1	2	3	4	
Getting on/off toilet	0	1	2	3	4	
Doing light domestic duties (cooking, dusting)	0	1	2	3	4	
Doing heavy domestic duties (moving furniture)	0	1	2	3	4	TOTAL

PATIENT SIGNATURE | DATE

REVIEWED BY PHYSICAL THERAPIST | DATE

WOMAC TOTAL SCORE /96

YAVAPAI REGIONAL MEDICAL CENTER
PHYSICAL REHABILITATION SERVICES

WOMAC OSTEOARTHRITIS INDEX
QUESTIONNAIRE

REHABILITATION SERVICES
PT THATCH WOMAC QUESTIONNAIRE
REV 11/05 (11/05)