MAC CLINICAL RESEARCH
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Participant Information Sheet (Part 2)

CONFIDENTIAL

Study Title: A Phase 1, Randomised, Double-Blind, Placebo-Controlled Study Investigating the Pharmacokinetics, Safety and Tolerability of Multiple Ascending Doses of a Revised Capsule Formulation of JNJ-39439335 (Mavatrep) in Healthy Participants and Patients with Knee Pain from Osteoarthritis

MAC Number:	MAC107
Protocol Number:	EPS-101
Principal Investigator:	[insert PI]
Study Site:	MAC Clinical Research [include site-specific address line 1] [include site-specific address line 2] United Kingdom
Sponsor:	Early Phase Services 19 Park Road Lytham St. Annes Lancashire FY8 1PW United Kingdom

Introduction

You have been invited to take part in a research study. The study is organised and funded by Early Phase Services (the **'Sponsor'**) and will be run by MAC Clinical Research. Early Phase Services is a UK-based company that is working to develop a treatment for pain.

Before you decide whether to take part in this research study, you need to understand why the research is being done, what it would involve for you, how your information will be used and the possible benefits, risks and discomforts. The study doctor, or a member of the research team, will go through this information sheet with you and answer any questions you may have. This process is called 'informed consent'.

Please take time to read the following information carefully. You may talk to your own family doctor or family, relatives and friends about the study if you wish. This information sheet will be split into the following parts:

- **Part A** tells you the purpose of this study and what will happen to you if you take part.
- **Part B** gives you more detailed information about the conduct of the study**.**

This information sheet may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand or if you would like more information.

Part A

What is clinical research?

Clinical research projects are performed as a way of bringing about progress in medicine and research. Clinical research projects make it possible to scientifically assess the properties of a drug, to demonstrate whether the drug is effective in managing or treating a specific disease/condition, to demonstrate the safety of the drug, and to learn more about a disease/condition and methods to diagnose and monitor it.

What is the purpose of this study?

The purpose of this study is to test a drug called JNJ-39439335, otherwise known as Mavatrep (the **'study drug'**) that is being developed for the treatment of pain.

Pain is a complex medical condition with multiple contributing factors. Pain is the most common reason for physician consultation in most developed countries and can have a strong impact on people's activities of daily living and quality of life. People experiencing pain often have depression, anxiety and sleep disorders.

Acute (short term) pain may require treatment for a few weeks. If acute pain is not effectively treated, it can lead to increased cost of therapy, prolonged hospitalisation and can progress to chronic (long term) pain. Chronic pain is generally the consequence of a disease or significant tissue damage. There are treatments to help prevent and manage chronic pain and make the condition easier to live with. Current treatments include painkillers (e.g., paracetamol and ibuprofen, or codeine/tramadol for more severe pain), antidepressants to ease pain, improve overall function and help with disturbed sleep, talking therapies such as cognitive behavioural therapy (CBT), heated pool therapy, pain management programmes and lifestyle changes, such as exercise programmes and improving sleep habits.

Neuropathic pain is caused by damage or injury to the nerves that transfer information between the brain and spinal cord from the skin, muscles and other parts of the body. The pain is often described as a shooting or burning sensation, which can come and go, but is often chronic. Unlike most other types of pain, neuropathic pain does not usually get better with common painkillers, such as paracetamol and ibuprofen, and other medications are often used. However, these medications can have a variety of undesirable side effects, including dizziness, tiredness and feeling 'drunk'. In addition, the currently available medications only have limited success in alleviating neuropathic pain; therefore, there is an unmet need for new treatments for neuropathic pain.

The study drug is a compound which is thought to be useful for treating pain. Seven clinical studies investigating single and multiple doses of Mavatrep, in a total of 176 healthy men and 70 men and women with osteoarthritis who were treated with Mavatrep, have been completed prior to this study.

Mavatrep has been investigated in people with osteoarthritis as these individuals often experience chronic and neuropathic pain, so are a good model in which to investigate how effective Mavatrep is in treating these types of pain.

The main aims of this study are:

- To assess the safety and tolerability of the study drug.
- To see how the body absorbs and removes the study drug.

This study will be divided into two parts: the study drug will be investigated in healthy volunteers in Part 1, and in people with osteoarthritis of the knee in Part 2. **This Participant Information Sheet and Informed Consent Form will cover Part 2 only.** To take part in Part 2 of this study, you must have moderate to severe osteoarthritis in one or both knees.

It is planned to enrol 8 participants in Part 2 of this study, who will be administered the study drug or placebo for 21 consecutive days. A placebo is a substance that looks, feels, and tastes like the study drug but does not contain the active ingredient. In this document, the term '**study medication**' refers to receiving either the 'study drug' (Mavatrep) or placebo. This is a double-blinded study, which means both you and the study doctor will not know if you have been given the study drug or the placebo. However, if a medical emergency occurs during the study period that requires knowledge of the treatment assigned to you, your study doctor and the pharmacist will be able to get this information rapidly.

In Part 2 of this study, 6 participants will receive the study drug and 2 participants will receive placebo, meaning that there is a 3 in 4 chance (75%) of receiving the study drug.

You will be administered two doses of the study medication on Day 1 and Day 2 (approximately 12 hours apart) in the MAC clinic. From Day 3 to Day 21, the study medication will be taken once daily (in the morning). From Day 3 to Day 13 and Day 16 to Day 20, you will take the study medication at home. During your visit to the clinic on Days 14, 15 and 21, you will take the study medication under observation by study staff.

The dose level of the study drug to be investigated in Part 2 of this study will be based on the study drug data from Part 1 and will not be any higher than the maximum safe dose determined in Part 1.

The study drug is 'investigational', which means that it has not yet been approved for marketing by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, or the Food and Drug Administration (FDA) in the USA.

Why have I been invited to participate?

You have been invited to participate in Part 2 of this study because you are an individual aged between 25 to 79 years, with a clinical diagnosis of osteoarthritis in one or both knees. If you do not have radiographic evidence of osteoarthritis of the knee (from either an X-ray, CT scan or MRI scan performed within 48 months prior to Screening) documented in your medical history, you will be required to attend for an X-ray as part of the Screening process.

You must be willing and able to stop taking any pain medication from at least 7 days prior to Day -1 (Visit 2) until the end of the study, and you must not have an occupation or hobby that puts you at greater risk of burning your skin.

You are also likely to match all the other characteristics required to enter this study.

Do I have to take part?

No, it is your choice whether to take part in this study. You should not feel pressured into joining the study. You do not have to decide today. You are free to leave and think about taking part. You may also discuss it with your own family doctor or family and friends. You may stop taking part at any time during the study; you do not have to give a reason why. This will not affect your regular medical treatment from your doctor.

What will happen to me if I take part?

Your participation in this study will last approximately 10 weeks and you will be required to take the study drug orally every day for a minimum of 21 consecutive days, either at the clinic or at home. You will also be required to attend the clinic for study visits on 11 occasions in total, consisting of a Screening visit to see if you are eligible and safe to be included in the study, 3 inpatient stays (1 × 2-night stay and 2 × 1-night stays) and 7 outpatient visits. You will also be contacted by telephone call on 3 occasions.

Following your Screening visit, you will attend the clinic on the day prior to your first day of dosing (Day -1) and stay until Day 2 (2-night stay). You will then return to the clinic for overnight visits on Day 14 until Day 15, and then Day 21 until Day 22 (2 × 1-night stays). You will attend outpatient visits on Days 23, 24, 25, 26, 27 and 35. The study team will also contact you by telephone call on 3 occasions throughout the study (Day 8, Day 18 and Day 31). The follow-up visit on Day 42 will complete your participation in the study. All visits will take place at the MAC clinic located in Manchester (please see a detailed Schedule of Events on pages 9 to 11).

Description of study assessments

The following assessments will be performed by the study doctor or a member of the study staff throughout the course of the study. The table below describes what you can expect for each assessment.

Assessment	Description
Confirmation of Eligibility	The study doctor will determine whether you are suitable to take part in this study.
Demographic Data	Questions about your age, sex, race and ethnic origin.
Medical History	Questions about your health including current or previous illnesses, allergies, conditions and surgeries. You will also be asked questions about any medications that you are taking now or have taken previously, including prescription drugs, over-the-counter medications, vitamins, herbal supplements and natural remedies. If you do not have radiographic evidence of osteoarthritis of the knee (from either an X-ray, CT scan or MRI scan performed within 48 months prior to Screening) documented in your medical history, you will be required to attend for an X-ray as part of the Screening process. Your GP will be informed of your participation in this study and will be contacted (with your permission) and asked to supply your medical history.
Alcohol Breath Test and Urine Drugs of Abuse Screen	Your breath will be tested for alcohol and your urine will be collected and tested for the use of opioids (pain relief medications), cannabis-like

Assessment	Description
	substances and other drugs of abuse. The use of these substances may put you at risk. We will not disclose the results of drug screens outside the clinic staff (or to your GP) without your permission. The only exception to this would be in extreme circumstances where you or the public would be at a significant risk if a piece of information is not disclosed. In the unlikely event of this situation arising, we would still endeavour to discuss with you first, if possible.
Blood Test for Hepatitis B and C, and HIV	It is important to know if you have been exposed to some specific viruses; for this reason, blood tests will be performed at Screening (Visit 1) to find out whether you have been exposed to the HIV virus, hepatitis B or hepatitis C. If the test does not identify any exposure to any of these viruses, you will continue the Screening process as usual. If the test shows evidence of exposure to the HIV virus, hepatitis B or hepatitis C, you will not be able to continue with the Screening process and you will be invited to meet our doctor. During this meeting with our doctor, you will be referred for counselling and follow-up at a Sexual Health Clinic convenient to your location for further assessments. If you test positive for HIV, hepatitis B or hepatitis C, with your permission we will inform your GP. We will report positive HIV, hepatitis B and hepatitis C test results to a local Sexual Health or Hepatology Clinic as it is important to let the Sexual Health and Hepatology Clinics know about the test result to get the necessary ongoing care either directly or indirectly through your GP. If you choose for any reason not to follow-up with the Sexual Health Clinic, Hepatology Clinic or your GP about the test results, it may still become necessary for us to inform them as you could potentially be putting others' health at risk. Again, you will be informed about this before doing so and a record will be maintained.
Pregnancy Test	If you are a female of childbearing potential, blood and urine pregnancy tests will be performed.
Blood Test to Assess Menopausal Status	If you are female, depending on your age and how much time has passed since you last had a normal/regular period, the study doctor may decide to perform an additional blood test to measure the levels of your FSH (follicle-stimulating hormone) to confirm you have stopped ovulating (i.e. that you are postmenopausal).
Burn Prevention Measures	Due to the mechanism of the study drug within the body, exposure to the study drug may decrease your ability to perceive dangerous/harmful heat. This could increase the risk of burns (please see section 'What are the side effects of the study medication?'), therefore, a list of Burn Prevention Measures that you should follow throughout the study will be reviewed with you at each study visit. This will ensure that you are aware of any changes in perception of heat that you may experience after administration of the study drug. You will also be supplied with thermometers to use at home. Once the Burn Prevention Measures have been explained to you at the Screening visit, you will have the opportunity to ask the study staff any questions. You will then be asked 10 questions to ensure that you understand the information. You must answer all 10 questions correctly to be able to take part in this study. If you do not answer all questions correctly the first time, you will have another opportunity to ask the study staff questions before taking the quiz again. You will also be questioned

Assessment	Description
	at each visit to ensure you understand each measure that you should follow. Burn Prevention Measures will include: · Check your smoke alarms regularly. · Reduce water temperatures. · Take extreme caution around open flames and sparks. · Avoid hot spills. · Store items designed to get hot, such as irons, straighteners or curling irons, unplugged and out of reach, and turn off items that create heat immediately after use. · Choose fire-resistant fabrics.
Burn Prevention Measures – Exit Interview	At the end of the study, you will be asked about the effectiveness of the Burn Prevention Measures that you followed throughout the study.
Rate Osteoarthritis Pain in Diary	At the Screening visit (Visit 1), you will be provided with a diary to take home with you which will be used to record a rating of your osteoarthritis pain out of 10 on each of the 7 days prior to Visit 2. You will be asked to bring the diary back to the clinic with you for Visit 2.
Questionnaire to Assess Suicide Risk	You will be asked to complete a questionnaire used to assess signs of suicide risk.
Questionnaire to Assess for Symptoms of Depression	You will be asked to complete a multiple choice questionnaire to evaluate key symptoms of depression. You will be unable to take part in this study if you are considered to be depressed.
Study Medication Administration	You will be administered two doses of study medication approximately 12 hours apart on Day 1 and Day 2. From Day 3 to Day 21, study medication will be taken once daily in the morning. On Days 1, 2, 14, 15 and 21, study medication will be taken in the clinic during your visit. On all other days (Day 3 to Day 13 and Day 16 to Day 20), study medication will be taken at home.
Vital Signs	Measurement of blood pressure and heart rate.
Body Temperature	Measurement of your body temperature, taken in your ear.
12-Lead ECG	Recording of the electrical activity of your heart. The ECG is painless and looks at how your heart is beating to check for any irregularities. Ten stickers with wires attached are temporarily applied to your chest, arms and legs to detect the electrical activity of your heart. You may be asked to shave your chest.
Blood and Urine Sampling for Safety Assessments	Tests to check your liver, kidneys and other body systems are working normally. Your samples (from which your identity cannot be directly determined) will be transferred to the safety laboratory for analyses, such as the numbers of red and white blood cells, as well as several liver and kidney function tests. The results will be available within a few days and your study doctor will inform you if any abnormalities are found.
Physical Examination	A medical check-up of your body by the study doctor. A full physical examination, including measurements of height and weight, will be performed at the Screening visit (Visit 1). A brief physical examination will be conducted at all other indicated timepoints, and when judged necessary by the study doctor.

Assessment	Description
Blood Sampling to Measure Study Drug Levels	Blood samples will be taken to see how the body absorbs and removes the study drug. At some visits, a cannula (small plastic tube inserted into a vein in your forearm using a needle) will be used for repeated blood sampling and will be removed after approximately 24 hours.

The assessments described above will not be performed at every visit. The table below shows what will happen at each visit.

Schedule of Events

	Visit 1	Visit 2				Visit 3			Visit 4		Visits 5, 6, 7, 8, 9, 10		Visit 11
	Screening	Inpatient Stay			Outpatient Period	Inpatient Stay		Outpatient Period	Inpatient Stay		Outpatient Visits	Telephone Call	Follow-up Visit
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day 13	Day 14	Day 15	Day 16 to Day 20	Day 21	Day 22	Days 23, 24, 25, 26, 27 and 35	Day 31 (±1 day)	Day 42
Approximate Duration	3 hours	3 days				2 days			2 days		1 hour	30 minutes	2 hours
Procedures and Assessments													
Confirmation of Eligibility	ü	ü											
Demographic Data	ü												
Medical History	ü[a]												
Alcohol Breath Test and Urine Drugs of Abuse Screen	ü	ü											
Blood Test for Hepatitis B and C, and HIV	ü												
Pregnancy Test (females only)	ü	ü											
Blood Test to Assess Menopausal Status (some females only)	ü												
Review of Burn Prevention Measures	ü	ü			ü[b]	ü		ü[b]	ü	ü	ü	ü[b]	
Burn Prevention Measures (Exit Interview)													ü
Rate OA Pain in Diary	ü[c]												

	Visit 1	**Visit 2**				**Visit 3**			**Visit 4**		**Visits 5, 6, 7, 8, 9, 10**		**Visit 11**
	Screening	**Inpatient Stay**			**Outpatient Period**	**Inpatient Stay**		**Outpatient Period**	**Inpatient Stay**		**Outpatient Visits**	**Telephone Call**	**Follow-up Visit**
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day 13	Day 14	Day 15	Day 16 to Day 20	Day 21	Day 22	Days 23, 24, 25, 26, 27 and 35	Day 31 (±1 day)	Day 42
Approximate Duration	3 hours	3 days				2 days			2 days		1 hour	30 minutes	2 hours
Procedures and Assessments													
Questionnaire to Assess for Symptoms of Depression	ü												
Questionnaire to Assess Suicide Risk	ü												
Study Residency													
Resident in Clinic		←	→			←	→		←	→			
Non-residential Visit	ü										ü		ü
Telephone Call					ü[d]			ü[e]				ü	
Study Drug Administration													
In-Clinic Administration			ü[f]	ü[f]		ü[g]	ü[g]		ü[g]				
At Home Administration					ü[g]			ü[g]					
Record Study Medication Administration in Your Diary					ü			ü					
Receive Paracetamol to Take Home				ü			ü						
Record Use of Paracetamol in Your Diary			←	→									

	Visit 1	**Visit 2**				**Visit 3**			**Visit 4**		**Visits 5, 6, 7, 8, 9, 10**		**Visit 11**
	Screening	**Inpatient Stay**			**Outpatient Period**	**Inpatient Stay**		**Outpatient Period**	**Inpatient Stay**		**Outpatient Visits**	**Telephone Call**	**Follow-up Visit**
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day 13	Day 14	Day 15	Day 16 to Day 20	Day 21	Day 22	Days 23, 24, 25, 26, 27 and 35	Day 31 (±1 day)	Day 42
Approximate Duration	3 hours	3 days				2 days			2 days		1 hour	30 minutes	2 hours
Procedures and Assessments													
Study Assessments													
Questions About Your Health and Any Medications You Have Taken	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü	ü
Vital Signs (blood pressure and heart rate)	ü	ü	ü	ü		ü	ü		ü	ü			ü
Body Temperature	ü		ü	ü		ü	ü		ü				ü
12-Lead ECG	ü	ü	ü	ü		ü	ü		ü	ü			ü
Blood and Urine Sampling for Safety Assessments	ü	ü				ü			ü				ü
Physical Examination	ü	ü								ü			ü
Blood Sampling to Measure Study Drug Levels			ü	ü		ü	ü		ü	ü	ü		ü

a If you do not have radiographic evidence of osteoarthritis of the knee (from either an X-ray, CT scan or MRI scan performed within 48 months prior to Screening) documented in your medical history, you will be required to attend for an X-ray as part of the Screening process.
b The study team will review the Burn Prevention Measures with you via telephone call on Day 8 (±1 day), Day 18 (±1 day) and Day 31 (±1 day).
c You will be asked to rate your osteoarthritis pain out of 10 on the 7 days prior to Visit 2 and record the scores in your diary.
d You will be contacted by telephone call on Day 8 (±1 day) during the first outpatient period. The telephone call will last approximately 30 minutes.
e You will be contacted by telephone call on Day 18 (±1 day) during the second outpatient period. The telephone call will last approximately 30 minutes.
f Twice daily dosing (approximately 12 hours apart).
g Once daily dosing (in the morning).

Will there be any additional tests or visits?

At the end of each visit, provided you are well and all your test results are appropriate, you may go home. If a doctor thinks it is necessary, you may be asked to remain in the clinic for further observation until any symptoms or test results have returned to normal.

On each visit you will also be asked about your general condition and any complaints you might experience (for example possible side effects of the study medication). If your problems require further investigation, additional tests will be done and additional visits (so called "unscheduled visits") might also be planned by your study doctor. Please report all unusual experiences, since they may be important.

What samples will be taken from me during the study?

The total amount of blood that will be taken from you during the study is 378 mL (approximately 21 tablespoons). If considered necessary, a cannula (small plastic tube inserted into a vein in your forearm using a needle) may be used for repeated blood sampling and will be removed after approximately 24 hours. Thereafter any samples will be taken by venepuncture (inserting a needle directly into a vein). The following types of samples will be taken from you during the study:

Reason for Sample	Type of Sample	What Will Happen to the Sample?
Samples to measure levels of the drug. These samples will be taken to measure the amount of drug in the body.	Blood	Your samples (from which your identity cannot be directly determined) will be transferred to MAC's laboratory in the UK, for analysis. These samples may be stored for future analysis as needed, including, but not limited to, looking at breakdown products of the drug. Your samples will be kept for 15 years.
Samples to check your liver, kidneys and other body systems are working normally.	Blood/Urine	Your samples (from which your identity cannot be directly determined) will be transferred to MAC's laboratory in the UK, for analysis. Your samples will not be kept.
To ensure that you are not pregnant (if you are a woman of childbearing potential).	Blood	
To ensure that you are not pregnant (if you are a woman of childbearing potential).	Urine	Your anonymised samples will be tested at the MAC clinic. Your samples will not be kept.
To assess for drugs of abuse.		

What do I have to do if I participate in the study?

- ECG Recording – Your heart function will be monitored throughout the study by ECG recording. Natural electrical signals coordinate contractions of the different parts of the heart. This keeps the heart beating and blood flowing. An ECG records these electrical signals to show how fast the heart is beating, the rhythm of the heart beats (steady or irregular) and the strength of the electrical signals. Changes in an ECG can be a sign of

many heart-related conditions. The ECG monitoring used in the study provides a method of early detection of such changes, so that proper treatment can be started.

- A standard or 'resting' ECG is one of the simplest and fastest tests used to evaluate the heart. Electrodes (small, plastic patches that stick to the skin) are placed at certain points on the chest and abdomen. The electrodes are connected to an ECG machine by wires. Then, the electrical activity of the heart can be measured, recorded and printed. No electricity is sent into the body.

You must agree to the following in order to participate in the study:

- **Study visits** – You will be asked to attend all scheduled study visits.
- **Administration of study medication** – You will be administered two doses of study medication in capsule form approximately 12 hours apart on Day 1 and Day 2. From Day 3 to Day 21, study medication should be taken once daily in the morning.

  On Days 1, 2, 14, 15 and 21, study medication will be taken in the clinic during your visit. On all other days (Day 3 to Day 13 and Day 16 to Day 20), study medication will be taken at home. Each dose should be taken with 240 mL of water following a 2 hour fast and all capsules must be swallowed within 5 minutes.

  Before leaving the clinic on Day 2 and Day 15, you will be provided with the doses of study medication that you will take once daily at home until your next clinic visit, as well as a paper diary to record your daily dose of the study medication (what time you took your dose, what time you had breakfast and what you had for breakfast). You will be asked to bring the diary with you to each study visit.
- **Previous medical history** – You must tell your study doctors and staff everything about your health history in an open and honest manner.
- **Use of medications**
  - **Before the study** – Please inform your study doctor about all the medications that you take, including herbal preparations and even those that you buy without a prescription (over-the-counter). You may not be suitable to participate in the study if you use certain medications. If you are suitable to participate, you will be asked to not take any prescription or over-the-counter medications throughout the study. Please consult with your study doctor before taking any new medications, either bought by yourself or on prescription from your own family doctor/GP before or during the study.
    - Use of any pain medication (apart from paracetamol for osteoarthritis knee pain, if needed) will not be permitted from at least 7 days prior to Day -1 (Visit 2) until the end of the study.
    - You must not have used topical capsaicin (e.g., creams or patches) within 7 days prior to first dosing, or intra-articular capsaicin (injected into a joint) within 1 month prior to first dosing.

- You must not have received any steroid injections into your knee joint within 3 months prior to first dosing, or into any other joint (e.g., shoulder) within 1 month of first dosing.
- You must not have received any hyaluronan injections into your knee joint within 1 month of first dosing.
- You must not have been administered any neurotoxin injections (e.g., Botox, Dysport or Xeomin) for at least 6 months prior to first dosing.

- **During the study** – During every visit, your study doctor or a member of the clinical team will ask you whether you have taken any medications since the last visit. Certain medications are allowed during the study, e.g., hormone replacement therapy (HRT) and paracetamol (up to 4 g per day) for osteoarthritis knee pain (if needed). Other treatments are not allowed, as they may affect your safety or the interpretation of the study results. Your study doctor will check this and will explain what is allowed and what is not allowed.
  - Paracetamol (up to 4 g per day) will be allowed throughout the study; it should be used **only** if you need additional pain relief for your osteoarthritis knee pain. Please record if you have used any paracetamol, the date and time of use, and how many tablets you have taken per day, in your diary.

- **Lifestyle** – Please avoid major changes in your exercise, diet and drinking habits during the study.
  - Strenuous exercise (e.g., long distance running, heavy lifting, weight training, aerobics) must be avoided throughout the study.
  - Please avoid exposure to excessive heat (e.g., saunas, steam rooms, sunbeds) or ultraviolet (UV) light which can increase the risk of burns following dosing and until the end of the study.

- **Diet** – While staying in the clinic, all meals and drinks will be provided for you. You must not eat any food other than that which is provided to you while you are in the clinic.

  You will be asked to fast (not eat or drink anything except water) for 2 hours before taking each dose of the study medication, until 2 hours after. Water will not be permitted 1 hour before and 1 hour after each dosing (except for the water used to swallow the study medication).

  In addition, you must also not eat any food for 4 hours prior to any visits where blood and urine samples are taken for safety purposes.

  As poppy seeds can sometimes cause a positive result on the drugs of abuse test, you should avoid eating poppy seeds/food containing poppy seeds for at least 48 hours before attending for any drugs of abuse test.

- **Alcohol** – You will be required to not drink alcohol for 48 hours prior to each visit and whilst resident in the clinic. Alcohol is allowed in moderation at other times during the study. You must not drink more than 28 units of alcohol per week if you are male, and 21 units per week if you are female. For example, one 25 mL measure of 40% spirit = 1 unit, one pint of 4% beer = 2.3 units and one standard glass of 12% wine = 2.1 units).
- **Smoking** – You must either be a non-smoker or not smoke more than 5 cigarettes per day (or equivalent e-cigarette use). You must not use tobacco and nicotine-containing products (including e-cigarettes, gum and nicotine patches) during your visits to the clinic.
- **Donation of blood or other blood products** – You must not donate blood or other blood products from 90 days prior to first dosing until 90 days after your final dose.

Could there be any harm to an unborn child or nursing infant?

Contraception

It is unknown if Mavatrep can harm an unborn baby. For this reason, you will be asked to use very effective contraception during the study.

If you are a male with a female sexual partner of childbearing potential, you must agree to use contraception in the form of a male condom from your Screening visit (Visit 1) until 90 days after your final dose. Additionally, you must not donate sperm from Screening until 90 days after your final dose. In addition, your female sexual partner of childbearing potential must use a highly effective method of contraception, from Screening until 90 days after your final dose (please see the list of accepted methods of contraception below).

If you are male and have had a successful vasectomy, then this will be accepted as a second form of highly effective contraception, in addition to you agreeing to use a male condom from Screening until 90 days after your final dose.

If you are a woman of childbearing potential, you must use a highly effective method of contraception from Screening until 90 days after your final dose, in addition to your male sexual partner wearing a condom. You must also have a negative pregnancy test at Visit 1 and Visit 2. Whether you are a woman of childbearing potential or not will be assessed at the Screening visit, and your study doctor will confirm the outcome with you.

The following are considered forms of highly effective contraception:

- Hormonal contraception (e.g., contraceptive pills),
- Implantable progesterone-only hormonal contraception,
- Using an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS),
- Bilateral tubal occlusion (sterilisation),
- Surgical sterilisation.

The female condom is not an acceptable method of contraception.

If you, or your female partner, does become pregnant during the course of the study or within 3 months after your final dose, we would ask you to tell your study doctor immediately. We will also ask if we can collect information about your or your partner's health and that of the baby.

There are no contraceptive requirements if any of the following are applicable:

- If you practice true abstinence, that is in line with your preferred and usual lifestyle. This must be practiced from Screening until 90 days after final dosing.
- If you are infertile (which may need to be confirmed).
- If you are a man and sexual activity is limited to a sole sexual partner who is a woman of non-childbearing potential (i.e., if they are postmenopausal or permanently sterile).
- Sexual activity is limited to a same-sex partner.

What are the possible disadvantages and risks of taking part?

Please see the '**What are the side effects of the study medication?**' section, which details potential side effects of the study drug.

Risks associated with drawing blood

As is common with blood drawing, you may feel some discomfort when the needle goes into your vein. In addition, you may experience light headedness or irritation, such as redness, tenderness and bruising at the sites used to obtain blood. Having a tube (cannula) placed in your arm for blood sampling can cause soreness, bruising, blockage of veins and (rarely) infection. These problems usually clear up within a few weeks. Blood tests can also make you feel faint, so we'll get you to lie down when we take your blood.

The swelling of a vein, or in very rare cases, a blood clot cannot be entirely ruled out. Infection is rare but could occur.

Risks associated with ECG

An ECG is a safe test. You may experience local skin irritations and redness from the stickers on your skin that will recover quickly.

If the ECG shows any adverse results, you will be referred to your GP or a cardiac specialist for assessment.

What are the side effects of the study medication?

All medications can cause side effects in some people. You must tell the study doctor or study staff about any side effects that you may experience. This is so you can be monitored to reduce the chance of you coming to any harm.

Seven clinical studies investigating single and multiple doses of Mavatrep, in a total of 176 healthy men and 70 men and women with osteoarthritis, have been completed prior to this study.

The following side effects have been identified from the current knowledge about the way the study drug works, animal studies with Mavatrep and clinical studies with Mavatrep:

- Moderate increases in body temperature have been observed within several hours after dosing with Mavatrep in previous clinical studies that resolved within 24 to 48 hours after dosing. Your body temperature will be measured frequently throughout the study, and you will be closely monitored for this side effect. If your body temperature changes significantly, you will stop taking the medication and will be monitored until it returns to normal.
- A decreased sensitivity to heat may be a potential side effect of the study drug. This was observed for up to 2 to 4 weeks after a single dose of Mavatrep in previous clinical studies. You should be very careful when touching hot objects, eating hot foods, or washing your hands or bathing with hot water. At the Screening visit, you will be asked a series of questions about burn prevention measures that you should follow throughout the study; you must answer all questions correctly to be able to take part in this study. If you do not answer all questions correctly the first time, you will have an opportunity to ask the study staff questions before taking the quiz again.
    - The list of burn prevention measures that you should follow throughout the study will also be reviewed with you at each study visit, and via telephone call between study visits, to ensure that you are aware of any changes in perception of heat that you may experience after administration of the study drug. You will also be supplied with thermometers to use at home. If your sensitivity to heat decreases significantly or you sustain a significant burn that is considered to be related to the study medication, you may be withdrawn from the study if deemed necessary by the study doctor.
- Disruption to your heart rhythm may occur following administration of the study drug. Your heart rhythm will be frequently monitored throughout the study using individual ECG recordings. In the unlikely event that your heart rhythm changes significantly, the study doctor will take the appropriate steps to reverse this side effect. This will mean you may be withdrawn from the study. If deemed necessary, you may be referred to the hospital emergency department and/or a cardiologist for further investigations and/or treatments.
- Administration of the study drug may affect the levels of certain substances in your blood, for example the number of red blood cells or the amount of haemoglobin (a protein found in the red blood cells that carries oxygen in your body). You will be closely monitored for these side effects with blood tests throughout the study.
- Administration of the study drug may affect the sensitivity of your nervous system to stimuli such as touch, temperature and pain. You may experience a decreased sensitivity to pressure on your skin (such as touching, brushing, pressure and vibration), a decreased sensitivity to temperature (warm and cold), a partial or total loss of sensation in part of your body (numbness), pins and needles, a burning or tingling sensation, or a prickling sensation in your skin. You will be closely monitored for these side effects throughout the study.
- The study drug's effect on the body may change when the drug is taken in combination with another drug, which can result in either a decrease or increase in the action of either, or both, drugs. This could have potential side effects. Therefore, the use of

certain drugs will not be allowed during the study. Your study doctor will explain what is allowed and what is not allowed.

You will be carefully monitored during your time on the study, although this does not mean these side effects could not occur. As with any drug, side effects that were not previously described may occur. You may also have an allergic reaction to the study drug. It is important that you report to the study doctor all symptoms and side effects that you may experience, as soon as they appear, whether or not you think they are related to the study medication.

Although all possible precautions are taken to prevent serious side effects, if such a side effect occurs, you may need to be admitted into hospital. Depending on the type of side effect, a medical specialist may be asked to take over your care.

What are the possible benefits of taking part?

This drug will not be available for use after you have completed the study and may not be available for use for many years following the study. There may not be any benefit to you, but you are contributing to the scientific knowledge which may lead to the expansion of treatment options for people with acute, chronic or neuropathic pain.

This completes Part A.

If the information in Part A has interested you and you are considering taking part, please read the additional information in Part B before making any decision.

PART B

What if new information becomes available?

During the course of the research project, new information may become available about the drug that is being studied, which might influence your willingness to participate in the study. If this happens, your study doctor will tell you about it and discuss it with you as to whether you wish to continue in the study. If you decide to withdraw from the study, your study doctor will discuss your options with you. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interest to withdraw you from the study. They would explain the reasons and arrange for your care to continue.

You have the right to know if, in the future, anybody plans to do any extra tests on your samples collected as part of this study. If we wish to undertake tests not mentioned here, then we would contact you for your specific consent.

What will happen if I don't want to carry on with the study?

You can stop taking part in this study at any time, without any consequences for you. No pressure will be exerted on you if you decide to stop participating at any moment.

If you decide to stop being part of the study, you should tell the study doctor immediately, who will ask you to come back to the clinic for a final visit.

Should you withdraw from the study then the information may still be processed along with any other data collected while in the study, but no new data will be added to the database. If you wish, you may ask for any samples that have been collected from you to be destroyed.

Under what circumstances would I be withdrawn from the study?

Your study doctor can take you out of the study even if you wanted to continue taking part if:

- The study is cancelled.
- The study doctor thinks that removing you from the study is in your best interests.
- You need extra medication that is not allowed during the study.
- You become pregnant during the course of this study.
- You are not co-operating, or you have not followed the directions given by the study doctor.

If you stop being part of the study for any reason, the study doctor may continue to use and distribute any information gathered in connection with you taking part in the study for the purposes described in this Participant Information Sheet/Informed Consent Form.

What if there is a problem?

Concerns

If you have a concern about any aspect of this study, you should ask to speak to a member of the research team who will do their best to answer your questions (see contact numbers provided at the end of this sheet).

Harm

If you become ill or injured due to your participation in this study, medical treatment will be provided as required in accordance with normal standards of medical care. The Sponsor has taken out study insurance and has agreed to provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking, the ABPI guidelines recommend that the Sponsor, without legal commitment, should pay compensation where the injury probably resulted from:

- A drug being tested or administered as part of the study Protocol
- Any test or procedure you received as part of the study

The Sponsor would not be bound by these guidelines to pay compensation where:

- The injury resulted from a drug or procedure outside the study Protocol
- The Protocol was not followed

Other exceptions and limitations on compensation may also apply. For further information, copies of the ABPI guidelines are available on request. Please speak to a member of the research team (see contact numbers provided at the end of this sheet).

The Sponsor does not provide compensation other than that described above. If you would like more information about compensation for research-related injuries, contact the study doctor.

DATA PRIVACY AND CONFIDENTIALITY

Why is my data being collected?

Your data is being collected by MAC Clinical Research on behalf of the Sponsor. MAC Clinical Research is a company that conducts clinical studies and processes the study data for Sponsors so that they can use this data to develop medicines and further scientific research. The lawful basis for processing your data is to ensure that MAC Clinical Research can carry out its legitimate interests, which include the conduct of clinical studies.

What will happen to my data during the study?

Your personal details and information from the study are processed by MAC Clinical Research in accordance with UK Data Protection law (Data Protection Act 2018), which is designed to protect your privacy. Your identity and other information obtained during this study will be kept confidential. However, information that does contain your identity may be disclosed in certain circumstances (see table below). If your data is transferred outside the UK, where this regulation applies, by a Sponsor or company associated with MAC, it will be contractually agreed between MAC Clinical Research and the Sponsor/company that the Sponsor will be

responsible for ensuring that your data will be protected in a manner that is consistent with UK Data Protection requirements.

The table below explains what data will be taken from you and what will happen to your data:

Type of data	Who has access?	Where can this be transferred to?
Personal data (for example, name, date of birth, address, passport details, NI numbers, ID, photograph, phone number).	MAC Clinical Research employees including physician, nurses, clinical assistants and administrators. Representatives of medicines regulatory authorities, members of ethics committees that approved the study or representatives of companies working on the Sponsor's behalf may inspect the study files and your medical records to ensure that the results of the study have been properly recorded. Companies working under contract to MAC in order to provide services such as analysis of blood samples.	Your personal data will not be shared with anyone outside of MAC. You will be assigned a study participant number to protect your anonymity. Your study participant number can be transferred to a company working with MAC who needs to perform a procedure (e.g., analysis of blood samples; MAC Clinical Research ensures this company complies with the UK Data Protection Act 2018).
Medical data (medical records).		Identifiable medical records will not be transferred outside of MAC.
Study data (information collected from Screening onwards) that can be used in reports of the study or for scientific presentation. Your personal details will be made anonymous.		This could be transferred to a third-party company working on the study outside of the UK. The Sponsor may also wish to use the information from this study as anonymous data for future medical research into as yet undefined scientific issues.

Your data may be stored for 25 years or more after the study has been completed, according to regulatory requirements. You will have the right to access and control the use of your medical records, together with your doctor, as allowed by national law. However, the study treatment will need to remain unknown until the study data analysis is completed.

You can obtain information on which treatment you have received after analysis and reporting of the study results. However, to ensure scientific integrity of the study, you agree that you may not be able to obtain this information until after the study has been completed. This may be many months after you have finished the study.

If you have any concerns or questions regarding the handling of your data, please contact the Data Protection Officer employed by MAC Clinical Research:

dataprotectionofficer@macplc.com

The Data Protection Officer
MAC Clinical Research
Kaman Court,
1 Faraday Way,
Blackpool,
Lancashire,
FY2 0JH, UK

Will my GP be informed?

Your GP will be informed of your participation in this study, and we will request information relating to your medical records from them. Your GP will be reimbursed for providing your medical records. If appropriate, your GP may be consulted about your treatment during the study.

If the serology blood tests during your Screening visit show evidence of exposure to the HIV virus, hepatitis B or hepatitis C, your GP will be informed with your permission. We will also report positive HIV, hepatitis B and/or hepatitis C results to a local Sexual Health or Hepatology clinic to enable you to get the necessary ongoing care required.

Can I take part in more than one study?

You are not eligible to take part in this study if you are currently enrolled in another study involving taking medication or have been enrolled in a different study within 30 days before the Screening visit (Visit 1). Each study has a washout period to ensure that any medication has sufficient time to leave the body. This means the number of studies a person can take part in is limited; this prevents interactions between experimental drugs. Washout periods also give the body time to recover from the sampling requirements of a study. So, we and other clinics like ours in the UK keep a database (The Over-Volunteering Prevention System) of healthy participants and some patients and we take a record of when they take part in studies. We will enter your details into the database, namely:

- your National Insurance number (if you're a UK citizen); or
- your passport number and country of origin (if you're not a UK citizen); and
- the date of your last dose of study medicine.

If you withdraw from the study before you receive any study medicine, the database will show that you never received a dose. Only staff at MAC and other medicines research clinics can use the database. We may call other clinics, or they may call us, to check your details. We'll keep your details for at least 2 years. If we need to contact you, we might be able to trace you through the information in the database.

What about insurance, tax and benefits?

If you have private medical insurance, you should let your insurers know you're going to take part in a research project. They will tell you if it affects your insurance.

Depending on your circumstances, you might have to pay income tax on your study payment. You should declare your income from studies to the HM Revenue and Customs (HMRC) every year – we won't do that for you. Occasionally, the HMRC ask us to give them information about volunteer payments.

If you claim benefits, you should declare your income from studies to the Department for Work and Pensions, because it might affect your benefit payments.

Business confidentiality

The information and any materials or items that you are given during the study - such as information identifying the research clinic, the Sponsor, any study drug(s), and/or the type of

study being performed - should be considered confidential business information of MAC and the Sponsor. You are of course free to discuss such information in confidence with your doctor or with your friends and family while considering whether to participate in this study or at any time when discussing your present or future healthcare. However, distributing confidential business information as described above to the media or posting it on the internet is strictly prohibited and by signature of this document you agree to this prohibition.

What will happen to the results of the research study?

The information about you will be kept anonymous. The results of this study will be disseminated (made public) following study completion; you will not be identified in these results. The results will then be used to develop the study drug and may be used to inform future scientific research into acute, chronic and neuropathic pain, and yet undefined issues.

The results of this study will also be available to patients and participants at the end of the study, and you may be provided a copy of the summary of results, if you so wish. The results may be published in the scientific press; however, you will not be identified by these results or within any published scientific literature.

A description of this clinical study will be available to on http://www.clinicaltrials.gov. This website will not include any information that may identify you. You can search this website anytime.

Who will cover the costs for my participation in the study? Will I be compensated?

You will receive a sum of £2010 if you complete the study (Screening, Visits 2 to 11 and 3 telephone calls) to compensate you for your time and participation in the study. If you are not found to be eligible for the study at Screening visit, you will receive £70. Travel expenses will be paid in addition to this (up to a maximum of £120) for each visit with documentation.

If you are asked to act as a reserve and are not used then you will be paid a sum of £120.

The following payment rules will apply:

- We won't pay you if you fail a test for recreational drugs or alcohol.
- If you do not follow rules or instructions given to you during the study, then you may be withdrawn from the study and you will not be paid.
- The payment is to cover your time, trouble and expenses. If we stop the study, if you don’t finish it for any other reason, or if we cancel one or more study visits, the payment may be reduced. If we cancel the study with less than 48 hours’ notice, before you have taken part in any study visits, we will pay you £100.
- If you choose to withdraw from the study, you will be paid for the visits you have attended and the commitment you have given to the study, up to the point you withdrew.
- If you have to come back for an extra unscheduled visit, we will pay you £25 plus travel expenses providing you have documentary proof of these.
- If we give you a place on the study but the tests before dosing show you are not suitable, we will pay you £70.

- Even if the Screening results show that you are suitable to take part, we can't guarantee you a place on the study. We will pay you £70 if you pass all the Screening tests but we can't offer you a place.
- Payments will be made around 30 working days after your very last visit, providing your results show you don't need any extra tests.

Who has reviewed and approved this study?

International guidelines exist to ensure that clinical studies are performed safely and ethically. These are called "Good Clinical Practice" and the "Declaration of Helsinki". All studies performed at MAC Clinical Research conform to these guidelines. All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by a recognised UK Research Ethics Committee and a government agency (the UK regulatory authority [MHRA]).

Further information and contact details

Thank you for reading this Participant Information Sheet. Remember, you do not have to take part in this research if you do not want to and you can stop taking part at any time.

If there is anything you do not understand or if you have any other questions, please ask your study doctor or a member of the study team.

If you wish to make a complaint, please contact the Site Director. Unresolved complaints may be escalated to an independent department, as appropriate.

Contact details: Study Doctor

Name:	[insert PI]
Address:	[insert site address] [insert site address] [insert site address] [insert site address]
Phone no:	[insert phone number]
Email:	[insert email address]

Contact details: Site Director

Name:	[insert Site Director]
Address:	[insert site address] [insert site address] [insert site address] [insert site address]
Phone no:	[insert phone number]
Email:	[insert email address]

Please call the above number within office hours (08:30 to 16:30) to speak to a study doctor or the same number outside office hours in an emergency to be redirected to the on-call doctor.

All spoken and written information and discussions about this study will be in English.

Do not sign the consent form unless you have had the chance to ask any questions that you may have and have received satisfactory answers. If you agree to take part in this study, you will receive a signed and dated copy of this Participant Information Sheet and Consent Form for your records.

Thank you for taking the time to read this information.

INFORMED CONSENT FORM

CONFIDENTIAL

Study Title:	A Phase 1, Randomised, Double-Blind, Placebo-Controlled Study Investigating the Pharmacokinetics, Safety and Tolerability of Multiple Ascending Doses of a Revised Capsule Formulation of JNJ-39439335 (Mavatrep) in Healthy Participants and Patients with Knee Pain from Osteoarthritis
Protocol Number:	EPS-101
Principal Investigator:	[insert PI]
Participant Number:	

	Participant Initials
I agree that I have been fully informed about all aspects of the study including information relating to confidentiality of my personal information and have been given ample time and opportunity to enquire about details of the study and decide whether or not to participate.	
I have read and understand the statements in the Participant Information Sheet Version 3.0, dated 10 December 2024 for the above study. All my questions about the study and my participation in it have been answered to my satisfaction. I am not currently participating in another study and have not participated in a study within 3 months.	
I freely and voluntarily consent to participate in Part 2 of this study and understand that I am free to withdraw at any time without giving any reason, without my legal rights being affected and I understand that the doctors or Sponsor may stop the study or my participation in the study at any time without my consent.	
I understand that if I withdraw my consent from the study, the Sponsor and study doctor may continue to use and distribute any data gathered during the study for purposes outlined in the Participant Information Sheet.	

I authorise the release of my medical records, for research or regulatory purposes to the Sponsors, Early Phase Services, the companies working on behalf of Early Phase Services, regulatory authorities, institution review boards, and study doctors, where it is relevant to my taking part in this research. I give permission to these individuals to have access to my records.	
I agree to my GP being informed of my participation in the study.	
I understand that I will receive a signed copy of this consent and authorisation form. I also understand that the original signed consent form will be filed with the study doctor.	
I understand the information given related to contraception and I agree to use highly effective contraception as stated in the Participant Information Sheet (if applicable). I agree to inform my partner of their contraceptive requirements (if applicable) during my participation in this study.	
I understand the information given related to HIV, hepatitis B and hepatitis C at the Screening visit and agree to proceed with the tests as stated in the Participant Information Sheet.	
I agree to my GP being informed of the results of my serology blood test if it returns a positive result for HIV, hepatitis B and/or hepatitis C. I understand that I will also be referred to the appropriate Sexual Health clinic, Hepatology clinic or my GP for further assessment.	
I have read and consent to my data being processed as explained in the section '**Data Privacy and Confidentiality**' in the Participant Information Sheet.	
I agree that my study data may be used as described in this consent form including transfer to countries outside of the UK, and my personal coded data may be archived for at least 25 years, consistent with regulatory requirements.	
I agree to thoroughly review and adhere to the Burn Prevention Measures throughout the study.	
I will let the study doctor know if I have any changes in medication, am injured, develop any illness, if I or my partner becomes pregnant, or if I plan to have an elective surgery or medical treatment procedure during the study.	
I agree to my study samples being stored and analysed for use on this study only as described in the Participant Information Sheet. If additional analysis is required, my samples will only be used if I consent to this.	

I understand that when volunteering to take part in this study I should not give up/turn down any offer of employment nor make any financial commitment on the expectation of receiving a study payment as I am not guaranteed a place on the study, and that occasionally studies are postponed or cancelled.	
I understand that a decision about whether I am considered eligible to participate in this study will be made after the study doctor has reviewed all the results from the Screening visit.	
I agree that I can be contacted in the future regarding the results of this study.	
I agree not to distribute this document, or the confidential business information described within it (including the research clinic details, the Sponsor, any study drug[s], and/or the type of study being performed), including but not limited to, the media or to post this information on the internet.	
I agree to take part in the above-mentioned study being conducted by MAC Clinical Research.	

I confirm with my signature that I have had enough time to read and understand the above information, and my questions have been answered to my satisfaction. I have the right to ask further questions as they come up during the study.

Written ICF:

PARTICIPANT:	
Printed Name:	
Signature:	
Time:.....:.....	Date:...../...../.....

PERSON OBTAINING INFORMED CONSENT:	
Printed Name:	
Study Role:	
Signature:	
Time:.....:.....	Date:...../...../.....