PATIENT INFORMATION & CONSENT DOCUMENT

PART 5 ONLY

Study Title:	A multi-part, adaptive Phase 1, first time in human study in healthy volunteers to assess safety, tolerability and pharmacokinetics (PK) following single ascending dose (SAD) and multiple ascending doses (MAD) of MTX325, including option to assess: a single dose in elderly participants; multiple doses in patients with Parkinson's disease (PD); Central nervous system (CNS) penetration, biodistribution, and biomarkers; and the effect of food on PK.
Simplified Title:	An adaptive first in human study of MTX325 in healthy volunteers and Parkinson's Disease (PD) patients
Protocol:	MTX325-101
IRAS ID:	1008552
Sponsor:	Mission Therapeutics Ltd
Investigator:	Name: _____
	Site No: _____
	Address: _____
	City/Postal Code: _____
	24 hour Tel No: _____

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with your friends and relatives. Please ask your study doctor or nurse to explain any words or items that you do not clearly understand. You may wish to talk to the doctor to discuss any part of this consent form in more detail. If you decide that you would like to participate, once you understand the study, then you will be asked to sign the consent form. You will be given a signed and dated copy of this form for your records. For your own health and wellbeing, you should give complete answers to questions from your study doctor or nurse. You will be asked questions about your medical history, current and past medications that you are taking, and about whether or not you are taking part in any other research studies or using any other experimental therapies or treatments.

This is a **five-part** study; this information sheet is for **Part 5** of the study only. Part 1 of this study was the first time in which MTX325 was tested in humans (known as a first-in-human study), but the drug has undergone comprehensive testing in what is known as the pre-clinical stage of drug development. This includes testing in animals and testing by other methods. Part 5 is commencing because earlier parts of the study (Parts 1–4 in healthy volunteers) have generated sufficient safety and tolerability data to support initiation of Part 5. Part 5 is therefore beginning based on the data available from the previous study parts. Thank you for taking the time to read this information document.

What is the purpose of the study?

The purpose of this study is to investigate the study drug MTX325.

The main objectives of Part 5 of the study are as follows:

- To assess the safety and tolerability (degree to which side effects of a drug can be tolerated) of MTX325 when it is given once or twice daily over a period of up to 28 days, and to compare this when two different dose strengths (amounts) are given.

- To measure the amount of MTX325 in the blood, how this amount changes over a period of time, and to compare this when different dose strengths are given.

- To investigate the amount of MTX325 in the fluid surrounding the brain and spinal cord (cerebrospinal fluid – CSF).

- To evaluate the effects of MTX325 on different aspects of mood e.g., overall mood state and risk of suicidal behaviour, to evaluate any improvement in symptoms associated with Parkinson's Disease (PD), and to see how these change over a period of 28 days.

As well as evaluating the above, we may also investigate, as exploratory objectives, the effect of MTX325 on the body by analysing the levels of certain biomarkers in the body. Biomarkers are markers within the body such as a gene, molecule or characteristic which can be used to identify the presence of a particular biological process occurring in the body or a particular disease. In addition, we will carry out imaging procedures at specific times during the study. This will include an FDG-PET scan using either a CT or MRI, depending on your site. This will be conducted twice, once at the start of the study and once at the end. You will have a separate MRI scan which will be conducted at the start of the study. The PET scan involves a small amount of exposure to radiation (further information about this can be found in the section titled 'What are the possible disadvantages and risks of taking part?'). Further to this, the samples collected during this study for measurement of biomarkers may be used to identify potential metabolites. Metabolites are by-products which are produced when a drug is broken down in the body and in the context of this study, the samples may be used for the analysis of specific markers such as dopamine and its metabolites. This information may be useful in future studies in patients.

Part 5 may also include an element of genetic testing/gene expression analysis where we will evaluate certain parts of your DNA (known as genes) which are involved in the processes that break down drugs (metabolism) in the body, and which may impact the way in which your body responds to the study drug. This evaluation (if undertaken) will allow us to determine whether differences in DNA between patients affects how your body responds to MTX325 or impacts the way MTX325 is broken down in the body which may affect the effectiveness of MTX325.

Part 5 is planned to consist of a maximum total of approximately 36 patients overall and split into two main groups; Group 1 and Group 2 (Group 1 of up to 12 patients receiving 20 mg once daily and Group 2 of up to 24 patients receiving 20 mg twice daily): each group receiving a dose of MTX325 which has been evaluated in the previous parts of the study (conducted in healthy volunteers). Each patient in each group will either receive MTX325 or a placebo (which contains no active drug) in the form of an oral capsule(s) and neither you nor your study doctor will know if you are taking MTX325 or placebo.

The purpose of the data generated in this study is to provide further information and guidance to support the study Sponsor in the development of the study drug MTX325, specifically to provide early data on the potential use of the study drug in the treatment Parkinson's Disease (PD). Further information about MTX325 may be found later on in this document. This study is sponsored by Mission Therapeutics Ltd, based in the United Kingdom (UK). For more information about the study Sponsor, you can visit the following website: https://missiontherapeutics.com/.

Why have I been chosen?

You are invited to participate as your doctor has determined that you may be eligible for this study as a patient with a current diagnosis of mild to moderate untreated PD.

What is the drug that is being tested?

MTX325 is being developed for the treatment of PD. In PD, it has been identified that there is dysfunction within a part of the cell known as mitochondria. The mitochondria are commonly referred to as 'the powerhouse of the cell' as they are responsible for the production of the energy in cells which allow the

cells to carry out their normal function and to trigger responses in the body. Mitochondria are constantly in a state of regeneration i.e., old mitochondria are removed from the cells and replaced with new mitochondria in order to keep the cells healthy and functioning. In normal functioning cells, this process occurs approximately every 40 days. This process where old mitochondria are removed is known as 'mitophagy'. In diseases where there is dysfunction in the mitochondria, this process can be disrupted such that the dysfunctional mitochondria are not removed from the cells. In the case of PD, this dysfunction leads to the accumulation of proteins within the neurons of the brain and subsequently, the death of these cells controlling the signals sent from the brain to the body controlling movement which results in the typical symptoms observed in PD.

Despite the development of effective therapies for PD, these treatments serve to manage the symptoms associated with PD and do not actually address the underlying cause of the disease. Over time, the current therapies can lose their effectiveness and therefore symptoms can become progressively worse, leading to increasing impairment and disability. Therefore, there is an unmet need to develop therapies which actively seek to target the underlying causes of the disease.

MTX325 is a compound which is classified as a selective USP30 (Ubiquitin Specific Peptidase 30) inhibitor. USP30 is a specific enzyme which works to slow down the process of mitophagy. An enzyme is a type of protein in the body which controls and regulates the speed of chemical reactions and processes in the body. As it has been observed that mitochondrial dysfunction is observed in PD patients, it is proposed that MTX325 may be helpful by inhibiting (slowing down or blocking) the activity of the USP30 enzyme. By slowing down or blocking the activity of USP30, MTX325 may help to increase the process of mitophagy in the cells, which in turn, increases the rate at which dysfunctional mitochondria are removed from the cells, and is expected to promote the overall normal functioning of mitochondria within the cell. The normal functioning of mitochondria may then help to reduce accumulation of the toxic proteins in the neurons of the brain and help to reduce the rate of progression of PD so that the condition can be managed more effectively. The data generated from this study will be used to support the future development and understanding of this study drug for future application in the treatment of PD.

Do I have to take part?

No. It is up to you to decide whether or not to take part and your participation is entirely voluntary. If you do, you will be given this information sheet to keep and asked to sign and date a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What are the possible benefits of taking part?

It is not known if you will have any clinical benefit by taking part in the study although we hope that the treatment will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with PD.

What will happen to me if I take part?

Part 5 of the study is a multiple-dose (MD), randomised, double-blind, placebo-controlled part of the study. The key terms of the study are described below:

Multiple-Dose (MD): In this study, the study drug (i.e. MTX325 or placebo) will be given once a day or twice a day for a period of 28 days in each group (Group 1 planned as once a day and Group 2 planned as twice a day) at a 20 mg dose strength for both groups which is a dose chosen based on the data generated in the previous parts of the study.

Randomised Study: This means that you will be randomly allocated to either receive the study drug (MTX325) or a matching placebo (containing no active drug). Based upon the number of planned patients for each group, you would have a 3 in 4 chance or 2 in 3 chance of receiving the active study drug i.e., for every three patients who receive the active drug in Group 1, one patient receives the placebo and in Group 2 for every 2 patients who receive the active drug, one patient receives the placebo.

Double Blind: This means that neither you nor the study doctor or study Sponsor will know whether you have been given the study drug or placebo. However, if the study doctor needs to find out what you have been given i.e., for safety reasons, they will be able to do so.

Placebo-controlled: A placebo, also known as a "dummy drug", is a product which looks identical to the study drug but does not contain any active drug. Within each study group, a small number of patients will receive the placebo, and the rest will receive the study drug (MTX325) in order to determine whether any effects observed are as a result of the study drug or are coincidental.

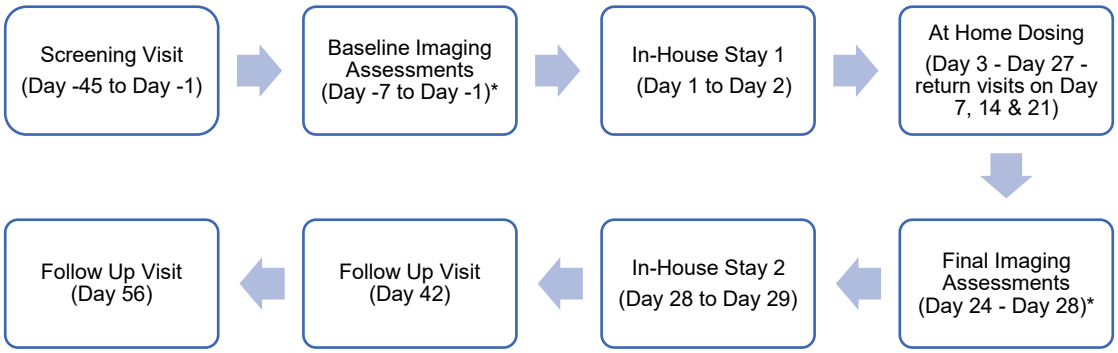
Part 5 of the study will proceed as follows:

For Part 5 Group 1 (up to 12 patients with mild-moderate untreated PD) – each patient will receive 20 mg of MTX325, or matching placebo once a day for a period of 28 days.

For Part 5 Group 2 (up to 24 patients with mild-moderate untreated PD) – each patient will receive 20 mg of MTX325, or matching placebo twice a day for a period of 28 days.

When the first six patients in Part 5 Group 1 have completed the full 28-days dosing and a minimum of 4 weeks of follow up, the data generated will be reviewed by a Data Monitoring Committee (DMC) to determine whether it is acceptable to move onto the remaining planned group in the study. In addition, once all 12 patients in Group 1 have completed, this review will be conducted again to confirm that it is appropriate to proceed with Group 2. Your participation in the study will last for approximately 14 weeks (from screening visit to final post-study follow-up visit).

Part 5 of the study will proceed as follows:



***Note:** the timing of the post-study follow up visit may be extended for all groups if the data generated during the study indicates that it is necessary to do so (you will be informed if this is to be the case and of when the post-study follow up visit will take place). In addition, the imaging assessments indicated on Day -7 to Day -1 i.e., FDG-PET and MRI are planned to occur on one day within this window where you will be required to attend the research site in order to have the imaging completed. However, as required, you may be asked to return on more than one day within this baseline window if your research site is not able to perform all scans on the same day. In any circumstance, you will be informed as to when you need to attend to have these imaging procedures completed.

Screening Visit (takes place within 45 days of the planned first dose)

If you decide to take part, screening tests will be performed to decide if you are eligible. You will be expected to read through this document (known as the patient information sheet) and if you are happy to do so, sign it under the supervision of a study doctor. You will be given as much time as required to ensure that you fully understand what is involved in the participation of this study. You will be given a copy of this signed document to keep. If you have given consent by signing this document, we will then perform a number of assessments to find out if you are eligible to take part.

The following assessments/tests will be performed:

* Once consent has been given, we will perform a review of the inclusion and exclusion (entry) criteria for the study with you to determine if you are eligible.

- We will record your age, gender, ethnicity, year of birth, height, weight, and body mass index (BMI).
- A brief medical examination will be performed where you will be asked questions about your medical history. This will include a review of any medication you are taking or have taken in the past.
- As applicable and if required, a COVID-19 test may be performed.
- Blood and urine samples for laboratory safety tests will be taken which will include a measure of your blood clotting.
- For females, we will use the blood sample for pregnancy testing and if you are a post-menopausal female, we will also use this sample to measure your levels of follicle-stimulating hormone (FSH) to confirm that you are post-menopausal.
- The urine sample will be used for drugs of abuse testing (such as cocaine etc).
- A measure of your vital signs (blood pressure, heart rate, breathing rate and temperature). These measurements will be taken twice, once in the sitting position and once in the standing position.
- A full physical examination will be performed by one of the study doctors to confirm that you are in generally good health (including an assessment of your spine to confirm that you are suitable to undergo a lumbar puncture procedure). This will also include an evaluation of the following body systems: ear/nose/throat, eyes, skin, heart, lungs, gastrointestinal, central nervous system, lymph nodes and musculoskeletal. If required, evaluation of other body systems may also be conducted.
- An electrocardiogram (ECG, a recording of the electrical activity of your heart).
- You will be asked to complete a Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire which is a series of questions to assess if you have suicidal thoughts or behaviours. The purpose of asking you to complete this questionnaire is to ensure that your mental health is stable before you are given the study drug and to assess whether you experience any changes in your mental health during the study. This type of questionnaire is used in some studies where the drug is targeting pathways within the brain as there may be potential with these types of drugs to cause changes in your mental health including increases in suicidal thoughts or behaviours. If you do experience such changes throughout the study, then you may be withdrawn from the study, and be referred to appropriate psychiatric services for treatment and care.
- You will be asked to complete a Montreal Cognitive Assessment (MoCA) which will assess different aspects of your cognitive function i.e., short term memory, spatial awareness, attention, concentration and working memory and language.
- You will be asked to complete a Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) which will assess various different aspects of your symptoms associated with Parkinson's Disease.

If you consent to be involved in this study, you must be willing to cooperate with the Investigator/study doctor and the study restrictions explained in this document. This includes agreeing to use the contraceptive methods described in this document. **Note:** these contraceptive restrictions apply to individuals of childbearing potential only.

Study Visits

If all of your screening assessments are satisfactory, then you may be invited to return to participate in the treatment phase of the study**.** During the treatment phase, you will be required to attend visits at the hospital/clinic and take doses of study drug at home. The following table shows the assessments following successful screening which will be performed at each visit within the baseline assessment period, 28-day dosing period and follow up-period up to Day 56. The exact days for visits are as follows:

Baseline Imaging Assessments – Day -7 to Day -1 (day visit(s) to the hospital/clinic within the stated window)

In-House Stay 1 – Day 1 to Day 2 (requires 1 overnight stay at the hospital/clinic and includes a lumbar puncture)

Home Dosing – Day 3 – Day 27

Return Visits – Day 7, Day 14 & Day 21 (single day visits to the hospital/clinic)

Imaging Assessments – Day 24 to Day 28 (day visit(s) to the hospital/clinic within the stated window)

In-House Stay 2 – Day 28 to Day 29 (requires 1 overnight stay at the hospital/clinic and includes a lumbar puncture)

Follow Up Visits – Day 42 and Day 56 (single day visits to the hospital/clinic)

Study Assessment	**Timepoint & Visit**
Eligibility Check	Day 1 (upon admission prior to dose)
Weight Check	Day 1 (upon admission prior to dose) Day 42 (during visit)
Review of Medical History	Day 1 (upon admission prior to dose)
Urine Sample for Drugs of Abuse Testing	Day 1 (upon admission prior to dose)
C-SSRS Questionnaire	Day 1: prior to dose Day 29: 24 hr post-dose Day 42: during visit
MDS-UPDRS Questionnaire	Day 1: prior to dose Day 28: during visit Day 42: during visit
MoCA Assessment	Day 1 & Day 28: prior to dose
Physical Examination (Symptom Driven)	Day 1, Day 7, Day 14, Day 21 & Day 56
Physical Examination (Full)	Day 28 & Day 42
Vital Signs (Blood Pressure, Heart Rate, Breathing Rate & Temperature) – sitting and standing	Day 1: prior to dose, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr & 12 hr post-dose Day 2: prior to dose Days 7, 14 & 21: during each visit Day 28: prior to dose, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr & 12 hr post-dose Day 29: prior to discharge

Study Assessment	**Timepoint & Visit**
	Day 42 and Day 56: during visit
12-lead ECG (recording of heart rhythm)	Day 1: prior to dose Day 2: prior to dose Days 7, 14 & 21: during each visit Day 28: 2 hr, 4 hr & 12 hr post-dose Day 29: prior to discharge Day 42 and Day 56: during visit
Blood and urine samples for laboratory safety testing (including measurement of blood clotting)	Day 1: prior to dose Day 2: prior to dose Days 7, 14 & 21: during each visit Day 28: prior to dose (blood clotting only), 2 hr, 4 hr & 12 hr post-dose Day 42 and Day 56: during visit
Pregnancy Testing	Day 1: upon admission (blood or urine sample) Days 7, 14 & 21: during each visit (urine sample) Day 28: upon admission (urine sample) Day 42: during visit (urine sample)
Study Drug Administration	Days 1-28: once or twice per day (depending on which group you are in)
Blood samples for determination of drug concentration – Pharmacokinetic (PK)	Day 1: prior to dose, 30 mins, 1 hr, 2 hr, 4 hr, 6 hr, 10 hr & 12 hr post-dose Day 2: prior to dose (24 hr post-Day 1 dose) Days 7, 14 & 21: during each visit (prior to dose) Day 28: prior to dose, 30 mins, 1 hr, 2 hr, 4 hr, 6 hr, 10 hr & 12 hr post-dose Day 29: 24 hr post-Day 28 dose Day 42 and Day 56 (during visit)
Blood samples for exploratory analysis (e.g. the effect of study drug on the body or a different method of measuring levels of the study drug in blood)	Day 1: prior to dose Day 14: during visit (4 hr post-dose) Day 28: 4 hr post-dose
Blood sampling for measurement of gene expression (in RNA)	Day 1: prior to dose

Study Assessment	Timepoint & Visit
	Day 14: during visit (4 hr post-dose) Day 28: 4 hr post-dose
CSF samples for determination of drug concentration and measurement of biomarkers including metabolites as applicable (obtained via lumbar puncture*)	Day 1: prior to dose Day 28: 4 hr post-dose (if possible)
MRI Imaging of the brain	Day -7 to Day -1: single scan on any day during the stated visit window
FDG-PET Imaging of the brain	Day -7 to Day -1: single combined scan on any day during the stated visit window Day 24 to Day 28: single combined scan on any day during the stated visit window **Note:** the PET scan may also include a CT or MRI scan imaging element as needed and dependent on the imaging procedure at each research site.
Blood Sampling during PET scan	Samples to be taken before, during the last 20 minutes of the scanning procedures and following scanning procedures
Blood Sample for Genetic Analysis (Optional)	Day 1: prior to dose

*****For further details regarding the lumbar puncture and imaging procedures, please refer to the study procedure section of this document which will describe this procedure in detail.

Note: you will be required to fast for at least 4-6 hours prior to the imaging procedures at all timepoints stated. If, following completion of the Day 56 visit, the study doctor believes that it is okay to do so, you will be discharged from the study, and your participation will be completed. If required, you may be asked to attend for further follow up visits with one of the study doctors. You should also be aware that if you are experiencing any side effects which require further investigations/tests or specialist treatment, then the medical team will refer you to an appropriate external medical team for these evaluations and treatment. This may include, referring you to your normal family doctor or referring you to an appropriate specialist doctor within a hospital. These external medical teams would then be responsible for carrying out the assessments and treatments as necessary.

Study Drug Dosing Procedure

You will be randomly allocated to receive either the active drug (MTX325) or a matching placebo (containing no active drug). The drug will be given as a capsule(s) which you can swallow with water and without regard to when you last ate i.e., no fasting required. Dependent on the dose strength you are taking, you may be required to swallow more than one capsule per dose. The capsules of MTX325 or placebo will be taken once or twice a day and following each dose, you are encouraged to remain in an upright position for at least 1 hour. You will take your doses of study drug each day from Day 1 until Day 28 and the final dose will be given on the morning of Day 28. If you are taking the study drug twice per day, the doses should ideally be taken 12 hours apart i.e., one dose of MTX325 or placebo in the morning and a second dose in the evening.

Home Dosing

As detailed above, other than the specific clinic visits, you will be required to take your daily doses of study drug at home. At the first clinic visit on Day 1 to Day 2, you will be given a set amount of study drug to take home with you which will include enough doses for the duration of the study. You will be informed how you should store and keep the study drug. When you are taking your doses at home, you should follow the same dosing procedure as described above. You will be asked to record the time of each dose in a specific diary which will be given to you by the research team. If you miss a dose, or if you take the dose outside of the indicated dosing time, you should record this information in your diary. **If you have a missed dose, then you must not take a double dose at the next dosing occasion to catch-up. Please contact the clinic if you are not sure.** The research team will also inform you of any other information which you will need to capture in the diary whilst you are not in the clinical unit. Please bring all of your used and unused study drug supplies (including any unused study medication and any relevant packaging or empty packets) and your completed diary to each clinic visit so that they can be checked by the clinical team.

What do I have to do?

It is very important that you carefully read this consent form and ask your study doctor all the questions that you may have. If you participate in the study, you will be asked to come to the hospital or the clinic at very precise times. It is important that you follow all instructions that are given to you, and that you let your study doctor know if you cannot come to the scheduled appointments, so that special arrangements can be made if possible.

You are not allowed to take part in this study if you are taking part in another study at the same time or if you have taken an experimental medicine up to 3 months prior to signing this consent form. In addition, if you have taken part in a study of a marketed drug (i.e., a drug which already available as a prescription or over-the-counter) within the 30 days prior to the first dose in this study, then you will not be able to participate.

If you are being treated by doctors other than your study doctor, you must inform them about your participation in this study. You will be provided with a personal study card that you should always carry with you. This card has important telephone numbers and information regarding this study. The information written on the card should be shared with any doctors, healthcare providers or hospitals if you seek medical treatment for any problem whilst you are participating in the study.

You may take your other regular medications during the course of the study, provided that they are classed as permitted medications. You should inform the study doctor about any medications, herbal products or supplements that you take prior to participation and while participating in the study even if they are prescribed by another doctor. You should also ensure that you consult the study doctor prior to taking new study medication, except in cases of emergency.

What are the alternatives for diagnosis or treatment?

There is currently no known cure for PD; however, there are a number of treatment options available. Treatment options range from changes in lifestyle and diet, administration of medications (which you may already be taking), different types of therapies such as physiotherapy, occupational therapy and speech therapy and in some cases, a type of brain surgery known as deep brain stimulation. You were offered participation in this study because your doctor thinks that you would be suitable. If you are unsure whether there may be another treatment for you then please discuss this with your doctor. Your study doctor can tell you more about other possible treatments and their side effects.

What are the side effects of any treatment received when taking part?

Like all medications that you take, there may be some side effects associated with taking MTX325. This is part of the first study to test MTX325 in humans and therefore, we have limited information on what the potential side effects could be. However, healthy male and female volunteers in previous parts of this study have already received doses of MTX325 (inclusive of single and multiple doses for a period of up to 14 days). In these volunteers, there were no safety or tolerability concerns identified at the doses planned for this part of the study. There was one serious event for one participant in Part 2 of the study which is summarised below (note that this event occurred at a higher dose level than is planned to be administered in this part of the study). In addition, two participants (one of whom was the subject who subsequently reported the serious event) experienced adverse events whilst on study drug which included a generalised rash a few days after starting treatment. The rashes were accompanied by other symptoms including

increased number of certain white blood cells, called eosinophils, certain raised enzymes which commonly come from the liver (called transaminases), sore throat, swollen lymph nodes, chills, loss of appetite, earache, fever, and cough.

In order for MTX325 to be considered safe to proceed into testing in humans, there have been a number of studies performed in the laboratory and in different animal species (known as pre-clinical studies). These studies concluded that there were no major safety concerns which would prevent dosing MTX325 to humans and there were no observed significant effects on any of the major body systems, such as the heart, lungs and central nervous system. In these pre-clinical studies there were, however, some effects observed at high doses which were considered to be related to the study drug. All of the effects were observed at doses which are considerably higher than the human equivalent doses which are planned to be given in this study and it is considered unlikely that they would occur at the doses used in this study; the effects included slight increases in heart rate and blood pressure, changes in heart rhythm, increase in pupil size and body temperature, hair standing on end and tremors across the various studies conducted in mice, guinea pigs and monkeys. In addition, some effects were noted in the studies conducted in monkeys in relation to a decrease in the numbers of a type of red blood cell called platelets (which are a cell type responsible for blood clotting); however, this effect resolved and returned to normal once dosing with the study drug was stopped.

As referenced above, during Part 2 of the study, there was one serious event reported for one participant which resulted in the diagnosis of a condition called Erythema Multiforme. This is a skin condition which can be caused by certain types of infections and as a result of a reaction to certain types of medicines. This condition produces a rash which initially appears on the hands and feet and can spread across the body, causing an itch or burning sensation. At this stage, it is not possible to know for sure whether this effect was as a result of the study drug or an underlying infection in the participant, and therefore, it is important that you are aware of this effect as a potential risk of receiving the study drug. As stated, the condition was reported in one participant only and resolved following a course of treatment

In order to minimise this risk in Part 5 of the study, the dose selected for Group 1 is lower than the dose administered which caused the generalized rashes and Erythema Multiforme. The selected dose is a dose where no side effects were reported or observed. Further to this, we will be performing safety assessments, such as blood and urine sampling, physical examinations, vital sign measurements and ECG monitoring to monitor for any potential effects observed. If any effects are noted, then the study may be stopped and if required, you may be referred for appropriate follow up treatment, as necessary

If you experience any side effects or new or unusual symptoms during or after the study, you should report them to your study doctor or the clinical staff, even if they are mild using the contact details provided on your emergency contact card. If you experience a side effect such as development of a skin rash, you should report this immediately to the study doctor or the clinical staff using the contact details provided as this is considered to be a side effect of special interest. In addition, we will be monitoring other specific side effects such as elevated levels of a blood cell called eosinophils and elevated levels of markers associated with liver function throughout the study.

Your study doctor and clinical staff will also be looking out for side effects and will be asking you how you are feeling throughout the study. If you have concerns about possible side effects, talk with your study doctor or any member of the study team. As with any drug, there is a potential risk of unforeseeable allergic reactions. These are generally very uncommon. A severe allergic reaction could be life-threatening or cause death.

Symptoms of an allergic reaction may include the following:

* Rash
* Having a hard time breathing
* Wheezing when you breathe
* Sudden drop in blood pressure

- Swelling around the mouth, throat, or eyes
- Fast pulse
- Sweating

If you experience any of the symptoms above whilst you are at home, then you should contact the clinical staff at the research site immediately using the contact details below. If your symptoms are severe, then you may contact 999 and seek immediate treatment. You should report any side effects to the clinical staff at the hospital/clinic.

How were the doses for Part 5 of the study chosen?

The dose for Part 5 of the study has been chosen based upon available data from the previous study parts (Parts 1-4), and it has been concluded that it is acceptable to progress to Part 5 of the study. The dose selected is less than a dose which was evaluated in the previous parts of the study and was shown to be well-tolerated. You will be informed prior to your first dose as to what dose strength has been chosen for your group.

What happens after Part 5 Group 1 has commenced and how do we decide if it is okay to move onto the next group (Part 5 Group 2) and which dose to give?

After the first six patients in Part 5 Group 1 have completed up to Day 28 and 4 weeks of follow up, the safety data generated will be reviewed by the Sponsor and other members of the study team (e.g., members of the Data Monitoring Committee which may include investigators/study doctors) to confirm there are no safety concerns and a decision will be made whether to proceed with the next group. Following completion of all of the patients in Group 1, this data will be reviewed again to confirm that the decision to proceed into Group 2 is supported. Decisions will be made based on the data to determine whether to progress as planned, or if changes to the study plan are required. Changes may include not proceeding with the next study group at all. It may also be determined that the timing or number of certain assessments within the study may be adjusted (either increased or decreased in frequency) and the timing of the post-study follow-up visit may be extended. Progression to the next groups will only occur if it is considered safe / appropriate to do so. If the safety data is not satisfactory then the next study group will not proceed.

What are the possible disadvantages and risks of taking part?

In addition to the possibility of experiencing side-effects, the possible disadvantages and risks of you taking part in the study are that you are going to have to have a number of routine tests performed that could be uncomfortable or painful. These are all to check whether the study drug is working and how it works in your body. Another disadvantage is that you will have several hospital visits to attend, which may disturb your daily life.

Study Procedures

Blood Sampling: A maximum total of approximately 500 mL of blood will be taken from you during this study. This is slightly more than is removed during a normal blood donation (approximately 470 mL). The volume to be taken will be spread over a period of time and we will monitor you for any potential side effects following blood sampling. This will include monitoring for any symptoms associated with low blood levels such as tiredness, fatigue etc.

If these effects are noted and are determined to be related to the blood sampling procedures for the study, then you may be withdrawn from the study. It is possible that you may feel some discomfort when the blood samples are being taken. You may also experience bruising, bleeding and/or soreness at or around the area of needle insertion. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it should resolve with time.

IMPORTANT: due to the volume of blood to be taken in this part of the study and the time period over which this blood is taken, you will not be permitted to participate if you have donated blood within the last 3 months prior to the screening visit. Further to this, it is important that you also agree that you will not donate blood for a further 3 months following completion of the post-study follow up visit.

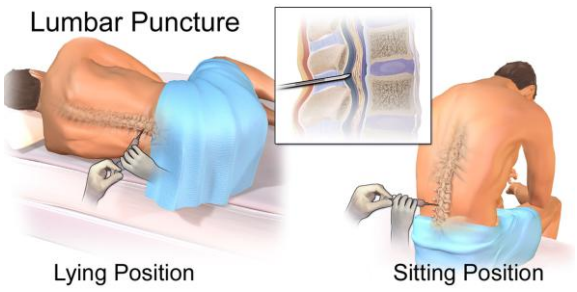
Cannulation: During the study, a cannula (small plastic tube) will be placed in your arm using a small needle. This will be used to allow us to take several blood samples without the need to insert a needle in your arm each time. This cannula will remain in place throughout each in-house stay (as applicable). There is a small chance of infection by placing the cannula in your arm, but every medical precaution will be taken to avoid an infection. You may also experience bruising, bleeding and/or soreness at or around the area of needle / cannula insertion site. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time. Please tell the study doctor or study staff if you do not feel well after having your blood drawn.

Blood Pressure and Pulse Rate: Your blood pressure and pulse will be measured using an inflatable cuff which will be placed on your arm. You may experience mild discomfort in your arm whilst the cuff is inflated.

ECG: Small sticky pads will be placed on your upper body before the ECG and an ECG machine will measure the electrical activity of your heart. Before the pads are applied, the skin needs to be cleaned. We may need to shave/clip small patches of your hair in these areas. Like a plaster these sticky pads may be uncomfortable to remove. You may have mild irritation, slight redness, and itching at the areas on your skin where the recording patches are placed.

Lumbar Puncture: During the study, you will be required to undergo two separate lumbar puncture procedures 28 days apart as shown in the image. This procedure will be carried out by a medical professional (trained/qualified healthcare professional) who is experienced and fully trained in carrying out this procedure. This is a test which is commonly carried out during routine clinical care.

During the procedure, a needle will be inserted into the lower part of your back in the space between two bones. You may be given a small amount of local anaesthetic into your back in order to numb the area before the needle is inserted, and the procedure itself is very similar to an epidural which is sometimes given to women who are in labour during childbirth. The needle will then be used to extract a small amount of the fluid which surrounds your spinal cord known as cerebrospinal fluid (CSF). This fluid will be analysed to measure the levels of MTX325 in this fluid as well as possibly looking for early indications of an effect of MTX325. This could be useful in the design of future studies to help determine if MTX325 is having a beneficial effect. This procedure may take between 30-45 minutes to complete and may cause some discomfort during and after the procedure. To try and minimise this, you will be asked to remain in a lying down position for approximately 2 hours after the procedure has been completed.



Common side effects of a lumbar puncture procedure include discomfort, irritation and bruising at the site of the needle insertion but this should resolve within a few days following completion of the procedure. Other typical side effects may include headache and discomfort which may last for a few days following completion of the procedure. In addition to the common side effects, there may also be some more rare and serious side effects which you should be aware of associated with the procedure. These effects include nausea/sickness, irritation of the nerves around the injection site (causing temporary numbness, tingling or pain in the legs), infection around the area of needle insertion and potential bleeding into the spinal area. However, it is important to note that this procedure will be carried out by a trained and experienced medical professional and every due care will be taken to minimise these risks. If you do experience any of these effects noted, you should report these to a member of the clinical team who will then be able to provide appropriate treatment and care as deemed necessary.

MRI Scan: If you take part in the study, you will have an MRI scan of your brain on one occasion (between Day -7 and Day -1). The scans to be performed do not expose you to any radiation and are painless. The MRI procedure will require you to lie still on a table for an extended period of time, in a noisy and narrow tunnel. If you have a fear of small or confined spaces, then you should consider whether you can take part in this study as all scanning procedures are mandatory for participation.

How does it work?

This scan uses a strong magnet and radio waves to take very detailed pictures of the brain. Unlike other scans, an MRI can also measure how much blood is flowing through different parts of the brain - without needing any injections or radiation.

What does it show?

It shows both the structure of the brain (its size, shape and any visible changes) and the blood flow to different brain areas, helping us understand how active those areas are.

What will happen?

Before you go into the scanner, you will be informed as to how long the scan is expected to last, this is typically around 30 minutes – 1 hour in total, and you will be asked to confirm that you are happy to lie still for that period of time. You will be asked to lie in the scanner while the images are taken. While the scanner is acquiring images it can be very noisy, so you will be given earplugs and/or ear defenders to wear. You may experience some minor side effects during the procedure including irritation in the ears due to the noise levels in the scanner or increases in temperature in your head and body due to the radio waves generated by the scanner. In very rare cases, if you are particularly sensitive, you may feel a 'tickling' sensation in your back or shoulders. This may be slightly uncomfortable, but will not be painful, and is not in any way harmful. During the procedure, you will be able to communicate with the team via an intercom in between the scans and if at any point during the scans, you wish to stop, you will be able to trigger an alarm system.

PET Scan: During the course of the study, you will be required to undergo an FDG-PET scan on two occasions (once prior to receiving the first dose on Day 1 and then once within 4 days prior to Day 28 or on Day 28).

How does it work?

The PET scan uses a small amount of radioactive sugar (FDG), known as the tracer. Cells that are more active, for example cancer cells, inflamed tissue, or activated brain areas take up more sugar. The PET scanner can detect this. As active cells use more sugar for energy, by tracking where the sugar goes, the scanner can show which areas are working harder than others.

What will happen?

Before the PET scan, you will have cannulas (a fine needle and tube) inserted. One of the cannulas will be inserted in a vein of your hand or forearm to inject the radiotracer into your body and the other cannula will be inserted into a vein in order to take blood samples during the last 20 minutes of the scan. The PET aspect of the imaging will follow immediately after the injection. The duration of the PET scan will last up to a maximum of 60 minutes. When having a PET scan, you will lie still on a table that slides into a tunnel slightly wider than your body. During the PET scan, your head will be secured using a headrest and foam padding. You may feel uncomfortable in the tunnel. However, the scanner is open at both ends, and you will be able to communicate with the research team during the PET scan. The scan can be stopped at any time at your request, but the scan may not be complete. If there are any abnormal findings from your PET scans, then you will be informed by the study medic who will discuss the finding with you, and with your agreement your GP will be informed.

Why are we performing this type of scan?

We are using this scan to look at how the brain uses energy (sugar) in people who have recently been diagnosed with Parkinson's disease. This helps us understand how Parkinson's may affect brain activity early in the condition. Changes in metabolism and blood flow in the brain may show us whether the drug is having a biological effect (an effect on the brain) - before the clinical/physical symptoms of Parkinsons Disease change. These scans may help see how the study drug might be working in the brain. The scans measure how the brain uses energy (FDG-PET) and how blood flows through it (MRI). By comparing the scans before and after treatment it may help us understand whether the drug affects brain activity or improves how certain areas of the brain function in Parkinson's disease.

Why are we collecting venous blood samples: Blood samples let us see how much of the study drug is in the bloodstream at that time. It helps show how the drug is processed by the body and whether it's

reaching the brain. Taken near the end of the scan, they can also help link blood drug levels with what's seen on the PET/MRI images for example changes in brain metabolism or blood flow.

Exposure to increased levels of ionising radiation (during imaging procedures):

If you take part in this study, you will have 2 PET scans. These will be extra to those that you would have if you did not take part in the trial. These procedures use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study will increase the chances of this happening by an additional 0.04%.

Insurance: If you have private medical insurance, you should let your insurers know that you intend to take part in a clinical study. They will be able to tell you if this will affect your insurance.

Test Results: There is a possibility that the tests performed during the study will find a medical condition which you did not know about. If this happens your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your GP.

COVID-19 Risks: You should also be aware of the risks of exposure to COVID-19. You will be required to follow any COVID restrictions and requirements that may be in effect nationally, regionally or in your hospital. This may include the wearing of masks and COVID-19 testing. You will be required to follow all current applicable self-isolation guidelines in the event of a positive COVID-19 test, which may impact your eligibility to continue in the study. Please ask your study doctor about what measures are in place at your clinic to reduce transmission between staff and patients.

Harm to the unborn child

For female patients of childbearing potential

It is not known if the treatment might harm the unborn child; therefore, you should not take part in this study if you are pregnant, breast-feeding or you intend to become pregnant during the period from the first dose (Day 1) until at least 90 days following the last dose of MTX325 (note that this period may need to be longer to also account for the time it takes for the levels of the study drug in the blood to half in value, in addition to a full sperm cycle). If you are a woman who might become pregnant, you will be asked to have a pregnancy test before taking part and at set timepoints during the study.

For male patients

It is not known if the study drug will affect sperm or semen and therefore you must not father a child during the period from the first dose (Day 1) until at least 90 days following the last dose of MTX325 (note that this period may need to be longer to also account for the time it takes for the levels of the study drug in the blood to half in value, in addition to a full sperm cycle).

Contraception Requirements

If you are a female patient of childbearing potential or a male patient with a female partner of childbearing potential, you must agree to use a highly effective method of contraception, in addition to a male condom during the period from the first dose (Day 1) until at least 90 days following the last dose of MTX325 (note that this period may need to be longer to also account for the time it takes for the levels of the study drug in the blood to half in value, in addition to a full sperm cycle). Highly effective methods of contraception include the following:

* Partner/female patient using oral contraceptive*

* Partner/female patient using injectable contraceptive

- Partner/female patient using implant/patch contraception
- Partner/female patient using intra-uterine device (IUD)
- Partner/female patient using intra-uterine system (IUS)
- Partner permanently sterilised
- Vasectomised male
- True abstinence - in line with usual lifestyle

*****Note that for use of the oral contraceptive as a highly effective method of contraception, this must be a contraceptive method which either contains both oestrogen and progesterone (synthetic man-made version of the hormones oestrogen and progesterone) or is a progesterone only pill which does have the ability to stop the process of ovulation i.e., the process by which the body releases the egg. By stopping the process for release of the egg, it is not possible to become pregnant. Certain types of the progestogen only pill (mini pill) do not stop the process of ovulation and therefore you should therefore tell the study doctor which type of oral contraceptive your partner is using so that they confirm this is an acceptable type in order for you to be eligible to participate in the study. All contraception methods should be continued for the periods outlined above.

Other Restrictions

If you are a male who has been sterilised or engage in non-vaginal intercourse you should use a condom to prevent exposure of semen to any partner (male or female) from the first dose (Day 1) until at least 90 days following the last dose of MTX325. In addition, for all male patients, you must not donate sperm from the first dose (Day 1) until at least 90 days following the last dose of MTX325. If your partner is already pregnant or currently breastfeeding, you must still use a condom from the first dose (Day 1) until at least 90 days following the last dose of MTX325. **Note:** all of the restriction periods noted above may need to be longer to also account for at least 5 half-lives of the study drug i.e., five times longer than the time it takes for the levels of the study drug in the blood to half in value, in addition to a full sperm cycle.

Pregnancy Reporting

For female patients and or male patients with a partner of childbearing potential: If you or your partner become pregnant during the course of the study (up to and including completion of the post-study follow up visit), you must tell your study doctor immediately so appropriate action can be discussed. You/your partner will be referred for specialist counselling on the possible risks to your unborn baby and arrangements will be offered to monitor the health of both you and your unborn baby. The Sponsor will also request your consent to collect confidential information about your/your partner's health and that of the baby up until delivery (additional follow up following this period may be required dependent on the outcome of the pregnancy).

What happens when the research study stops?

Following your post study follow up visit, if the results are acceptable to the doctor, you will be discharged from the study. If you have any side-effects that have not yet resolved, you may be required to attend the unit for follow-up tests. There are no additional planned procedures for follow-up after the end of the study. You will not be able to carry on taking MTX325 after the study has finished. There is a possibility that in the future, the Sponsor may wish to conduct additional exploratory future analyses on some of the samples collected from you during this study. It is important to note that this additional analysis will not require you to give more samples; the analysis will be conducted using the remainder of the samples which will be collected from you during the study. The purpose of this is to support the future development of MTX325. As part of this document, you will be asked to give consent in order for the future analysis of these samples to be undertaken as required. This exploratory future research is entirely optional, and you retain the right to refuse consent. If you do not wish to consent to the future research, you will still be able to participate in

the study. This document provides full details of what will happen to your samples. All other data collected will be stored for at least 25 years after the end of the study and copies of these data will also be provided to the Sponsor (Mission Therapeutics Ltd).

Details of who may have access to this data and what might happen to this data during this time are provided in this document. You will be told if any new analyses on any of your samples or data is planned in the future. You will be asked to give your consent for the additional analyses. You retain the right to refuse consent.

What if relevant new information becomes available?

Sometimes during a study, we receive new information about the study drug. If this happens your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide not to carry on, your study doctor will make arrangements for any follow up assessments required. If you decide to continue in the study, you will be asked to sign an updated consent form. On receiving new information your study doctor may consider it to be in your best interests to stop the study. They will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and any required follow up assessments will be arranged.

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

If you withdraw from the study, you are advised that any data and samples collected up to the point of your last visit will be analysed, reported and provided to the Sponsor in line with this ICF. No further information will be collected after your last visit. Even if you decide to stop participating in the study, for your own safety, you are encouraged to attend the follow up visits as advised by your study doctor. For the optional samples, you may ask that these samples be destroyed.

Expenses and payments

You may receive payment for some of your time in this study. Any payment which you receive will be determined by the clinical site and will be a payment which is considered to be acceptable for the requirements of the study and potential loss of income as a result of your participation. Payments may be issued as follows:

- Payment for completion of procedures such as lumbar puncture and imaging - £130 per procedure
- Payment for time lost through visits:
    - Day 1 and Day 28 In-house stay - £200 per visit
    - All other visits - £100 (includes refreshments, excludes separate imaging visits as paid separately).
- Payment for full diary completion - £20
- Reimbursement for travel costs and other expenses incurred while attending visits - £130 per patient per visit for any costs related to travel

These payments are subject to condition and as per the standard procedures at your research site. To note, if you are participant on a zero-hours contract and can provide reasonable evidence of loss of earnings as a result of study participation, then you would be reimbursed on the basis of your hourly rate. In addition, the Sponsor may reimburse for reasonable travel costs for a single caregiver where significant travel and overnight stay is required, and assistance is required for patient safety or support.

Insurance

If you have a concern about any aspect of the study, you should speak to your study doctor. If you develop side effects, these will be treated at no charge to you. If you have private medical insurance, you should let your insurers know that you intend to take part in a study. They will be able to tell you if this will affect your insurance. The Sponsor will provide compensation for injury and suffering whenever a relationship with taking part in the study is demonstrated. If your health or wellbeing worsens significantly **as a result of taking part in the study**, the Sponsor will compensate you. This is regardless of whether you can

prove fault on the part of the Sponsor (or anyone else connected with the study). The amount of compensation may be reduced if you are partly responsible for the injury. The amount of compensation may also be reduced if you are separately compensated under any other insurance policy. The Sponsor will follow the compensation guidelines outlined as per each country specific legislation. If you are not sure about any of the information above, or wish to make a claim, you should contact the study team.

Will my taking part in this study be kept confidential?

How will we use information about you?

We will need to use information from you, from your medical records, your GP and other sources applicable for this research project. This information will include your initials, name, contact details including phone number and email address, home address and other identifiers which do not directly identify you because it uses a number code (encrypted). People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. Mission Therapeutics Ltd. is the Sponsor of this research and is responsible for looking after your information.

We will keep all information about you safe and secure by:

* Access to your personal data is given to your study doctor and other staff involved in the study or your medical care in general. Your personal data is protected against unauthorised access.

* Only authorised representatives of Mission Therapeutics Ltd. the study Sponsor and agents of national health authorities may inspect your personal data as necessary or required to verify the proper conduct of the study. This access to personal data can only occur at the study site or remotely (via secure systems at the hospital or clinic) and these persons are subject to a strict secrecy obligation.

* With regards to the encrypted data, the code is strictly separated from your records. Any transfer of data outside the study site, in particular to Sponsor, its affiliates and its contractual partners, takes place only in encrypted form. Your encrypted data may be transmitted to countries which do not have the same level of data protection as within the European Economic Area and the United Kingdom (for example countries such as but not limited to the United States of America and Canada). However, this data will be protected by corporate rules and binding contracts and will not be able to be traced back to you.

International Transfers

We may share data about you outside the UK for research related purposes to:

* Additional research purposes and may be combined with other databases for such purposes.

If this happens, we will only share the data that is needed. We will also make sure you can't be identified from the data that is shared where possible. This may not be possible under certain circumstances – for instance, if you have a rare illness, it may still be possible to identify you. If your data is shared outside the UK, it will be with the following sorts of organisations:

* Partners working on behalf of the study Sponsor who analyse your data

* Organisations who store your data

We will make sure your data is protected. Anyone who accesses your data outside the UK must do what we tell them so that your data has a similar level of protection as it does under UK law. We will make sure your data is safe outside the UK by doing the following:

* Some of the countries your data may be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK

* We use specific contracts approved for use in the UK which give personal data the same level of protection as it has in the UK. For further details visit the Information Commissioner's Office (ICO) website

* We do not allow those who access your data outside the UK to use it for anything other than what our written contract with them says

* We need other organisations to have appropriate security measures to protect your data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your data against accidental loss and unauthorised access, use, changes or sharing

* We have procedures in place to deal with any suspected personal data breach. We will tell you and applicable regulators when there has been a breach of your personal data when we legally have to. For further details about UK breach reporting rules visit the Information Commissioner's Office (ICO) website

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. We will keep your study data for the minimum period of time required by UK law. Currently, your data will be stored for 25 years after the end of the study or, if longer, until the end of 2 years after marketing authorisation approval for the study drug. The study data will then be fully anonymised and securely archived or destroyed.

What are your choices about how your information is used?

* You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

* You have the right to ask us to remove, change or delete data we hold about you for the purposes of the study. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this.

* If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

You can find out more about how we use your information, including the specific mechanism used by us when transferring your personal data out of the UK by using the following:

* by asking one of the research team

* by contacting our UK data protection representative

The Sponsor has an appointed data protection representative; however, in the first instance, if you have any data protection queries, then please contact your study site and as appropriate, your queries will be discussed with the Sponsor representative.

If you have any questions about the handling of your data in this clinical trial, please contact your study doctor. If necessary, persons responsible for data protection at the Sponsor or at the Site may be contacted by your study doctor.

You can find out more about how we use your information at:

- https://www.nhs.uk/conditions/clinical-trials
- by asking our research team

You also have the right to file a complaint with the Information Commissioner’s Office in the UK regarding the handling of your data:

The Information Commissioner’s Office

Water Lane, Wycliffe House, Wilmslow, Cheshire SK9 5AF.

Email: casework@ico.org.uk; Telephone: 01625 545 700

Involvement of your GP/Family Doctor

If you decide to take part in this study your GP will be informed of your participation and of any relevant medical findings. In addition, a copy of your medical history may be provided to the medical team from your GP in order to confirm that you are eligible to participate in the study.

What will happen to the results of the research study?

Your data will be analysed by Mission Therapeutics Ltd or other companies acting on behalf of Mission Therapeutics Ltd to see how the drug has worked in you and the other people in the study. You should also be aware that the Sponsor/owning company of MTX325 may not always be the current Sponsor Mission Therapeutics Ltd and therefore, as required, the data from this study may be shared with these entities as applicable. Your data may be analysed in any country world-wide. Certain statistical tests will be carried out on your data, along with that collected from the other patients who entered the study. Mission Therapeutics Ltd may forward the results of the study to health authorities world-wide, and the results may also be used in reports of the study or scientific presentations or publications. In addition, following completion of the analysis of the study results and the compilation into a formal study report, you will be provided with a brief summary of the outcomes of the study. This summary will be provided to you via email or via post.

What will happen to any samples I give?

Any samples (such as blood or urine) which are used for the purposes of safety testing will be analysed by your local hospital laboratory or at a selected central laboratory chosen by the study Sponsor. All other samples collected during the study will be sent for analysis to suitably qualified laboratories chosen by the study Sponsor who may be based anywhere worldwide. In addition, if required, the samples may be sent for additional analysis by another suitably qualified laboratory chosen by the study Sponsor who may be based anywhere worldwide. All samples (with the exception of the genetic testing samples) mentioned above will be analysed and stored for a period of up to 5 years by the Sponsor after the clinical study report for the study and main analysis has been finalised and completed. With respect to the genetic sample (inclusive of the gene expression samples), the samples will be stored for an extended period of time until such time as the drug has received its' first marketing approval in a country or until such time as the drug has stopped clinical trials. The purpose of this is to hold these samples for a sufficient period of time in case there is need to conduct further analysis due to the way in which MTX325 acts on the body.

These samples will be coded with a unique identifier with no personal information included which could identify you as an individual. Equally, some of the samples have been processed in such a way which removes any cells which may contain DNA and therefore these samples could not be analysed in a way which could identify you as an individual. Other samples which are collected in the study may contain small traces of cells which contain DNA; however, with the exception of the genetic sample and gene expression samples, the samples will not be analysed with the intention of analysing your DNA, these samples will purely be analysed for the purposes described in this document to support assessing the objectives of the study.

All of the analysis described above is considered mandatory (inclusive of the genetic testing and gene expression analysis) and if you do not wish to consent to this analysis, then you will not be able to participate in the study. All of the data mentioned above will be stored in a form which is not personally identifiable i.e., using only the patient number assigned to you during this study. In addition, you should note that any of the samples used during the study may be used for the purposes of conducting method validation exercises, developing quality controls and performing standard calibration exercises associated with the methods used for the analysis of the samples collected during the study.

OPTIONAL FUTURE RESEARCH

Once the main analysis on the samples collected during the study has been completed, the Sponsor may wish to conduct further exploratory research to support the future development of MTX325 using any of the samples collected during this study. Your samples will remain coded with no personal information to identify you. As part of this document, you will be asked to give consent in order for this future analysis to be undertaken as required. This exploratory future research is considered entirely optional and therefore, if you do not wish to consent to this, then you will still be able to participate in the study. If you don't consent, your samples will not be used in any future research and will be destroyed following the 5-year storage period or extended storage period (if in relation to the genetic analysis sample). This exploratory analysis

may take place at a suitably qualified laboratory chosen by the study Sponsor and will be undertaken during the 5-year storage period or extended storage period (if in relation to the genetic analysis sample) where they will be held by the study Sponsor. You will be informed if testing on your samples for this study will change.

Will any genetic tests be done?

During this part of the study, the Sponsor may wish to conduct genetic analysis and gene expression analysis. This analysis will only be carried out if the data generated during the study shows sufficient variation between patients in this part of the study which could indicate that individual variations in patients' DNA may have some effect on the way in which MTX325 is broken down in the body or the response to the study drug (applies to genetic analysis only). The gene expression analysis may be carried out as applicable. You will be asked to provide a blood samples at various timepoints during the study which will be used to undertake this exploratory genetic analysis. Blood samples will be stored and may be shared with relevant parties, but the samples will not be provided with identifiable information. A gene is a sequence of letter codes which provide the instructions for the building of proteins in the body. It has been identified that certain genes are responsible for producing proteins that determine how your body responds to drugs or how drugs are broken down/metabolised in the body. These genes can have subtle changes and differences between individuals which can affect how the drug acts in the body and how your body breaks down the drug. These changes could increase or decrease the effect of the drug or could cause your body's response to the drug to be impacted. The effect of this could result in certain individuals requiring higher or lower doses of the drug to produce the same therapeutic effect or could mean that certain individuals would not respond to the drug at all. Therefore, the Sponsor would like to include the option to perform genetic analysis on patients in this part of the study to evaluate whether differences in DNA have an effect on the activity of MTX325 and how the body breaks down MTX325. The taking of these samples is considered mandatory for your participation in the study. Therefore, if you didn't wish to provide consent for these samples to be taken, you will not be able to participate in the study.

If you do consent, this analysis will be performed if required by the study Sponsor in order to understand the impact of genetic factors on the effect of MTX325. Understanding these effects may be required in order to support the future development of the drug before proceeding with future research in patients with PD. All genetic analysis if required will be undertaken by a suitably qualified laboratory chosen by the study Sponsor. Samples will be coded with a unique identifier. However, we would acknowledge that these samples do contain your DNA and therefore it is possible for you to be identified as an individual. Results from this genetic analysis will not be shared with any the Site or with you as a research patient. The rationale for this is that the results are purely for research use only and only for the purposes of exploring and identifying genetic factors or variations between individuals which could impact any one individual's response to MTX325. Any additional information which is identified within this process will not be shared, nor will it be recorded as part of the data analysis for the study. All of the data collected during this exploratory analysis will not be shared with any agencies or parties outside of the study Sponsor and will only be used for the purposes of understanding how differences between individuals' DNA affects the activity and breakdown of MTX325. As referenced above, the sample will be stored and retained by the Sponsor for an extended period of time until such time as the drug has received its' first marketing approval in a country or until such time as the drug has stopped clinical trials. The purpose of this is to hold these samples for a sufficient period of time in case there is need to conduct further analysis due to the way in which MTX325 acts on the body.

Who is organising and funding the research?

The study is funded and Sponsored by Mission Therapeutics Ltd. The Sponsor of the study will pay the Site and the investigator for the time they spend on this study.

Who has reviewed the study?

This study has been looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. The study has been reviewed and given a favourable opinion by Wales REC 2 Research Ethics Committee. This study has also been reviewed and given approval by the Medicines and Healthcare products Regulatory Agency (MHRA), the main UK drug regulatory body.

Who can I contact if I have any further questions?

If you have any questions about the clinical study or about your rights and obligations as a patient, you can contact at any time the study doctor whose name appears on Page 1 or any other study doctor at any time. If you experience any symptoms, adverse effects or injury during the study, please inform your study doctor. In an emergency, please contact your study doctor on the number mentioned on Page 1 of this document.

INFORMED CONSENT FORM

Title of the Study

A multi-part, adaptive Phase 1, first time in human study in healthy volunteers to assess safety, tolerability and pharmacokinetics (PK) following single ascending dose (SAD) and multiple ascending doses (MAD) of MTX325, including option to assess: a single dose in elderly participants; multiple doses in patients with Parkinson's disease (PD); Central nervous system (CNS) penetration, biodistribution, and biomarkers; and the effect of food on PK.

Study No.: MTX325-101 Screening-No.:

IRAS ID: 1008552

Patient: ..... Date of birth |__|__| |__|__| |__|__|
Name of the Study Patient Day Month Year

.....
Name of Study Doctor

The following consent form will be signed by the patient to confirm consent:		
		Please initial Box
1.	I confirm I have read (or someone has read to me) and understood the information sheet for the above study. I understand the possible risks and benefits of the study and the other treatment options available to me. I have had enough time and had a chance to ask questions. I have received satisfactory answers to all my questions.	
2.	I understand that any significant new information that comes out during this study, and that might affect my health and wellbeing in any way, will be given to me in a timely manner.	
3.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by representatives of Mission Therapeutics Ltd (the study Sponsor), from regulatory authorities or from the hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I agree that data (in an anonymised format) about me relating to this study may be sent to countries that do not have data protection laws similar to those in the UK.	
4.	I agree that my pseudonymized clinical data may be shared with The Michael J. Fox Foundation for Parkinson's Research (the study funder). This data may be kept for storage at a central controlled-access data repository either hosted by The Michael J. Fox Foundation, its collaborators, or consultants and will be kept for as long as storage of such data is justified in accordance with applicable law. To advance scientific discoveries, your pseudonymized data will be made available under controlled access for the intended use of research in Parkinson's disease as well as other biomedical research studies that may not be related to Parkinson's disease.	
5.	I understand that for my safety, it is important that I provide the study doctor with all information about my medical history.	
6.	I agree to follow the study doctor's instructions and will notify the study doctor immediately if I believe that I have any new symptoms or side effects.	
7.	I understand that I will receive a signed and dated copy of this consent form.	

8.	I acknowledge that my personal data will be collected, stored and evaluated during and after the conduct of the study as described in this document.	
9.	I agree that the samples I donate as part of this study will be stored and analysed as detailed and understand that these may be provided to relevant collaborators in support of the conduct of this research.	
10.	I understand that my participation is voluntary and that I am free to withdraw from this study at any time, for any reason, and my decision will not affect my future medical care at this facility.	
11.	I agree to my GP/family doctor being informed about my participation in the study.	
12.	I give consent for the performance of the lumbar puncture procedure to be performed. I understand the risks associated with the procedure; the limitations of the testing and the implications of any test result I may receive.	
13.	I give consent for the performance of the imaging procedures (including FDG-PET and MRI). I understand the risks associated with the procedures; the limitations of the testing and the implications of any test result I may receive.	
14.	I have had the study restrictions (including contraception) explained to me and agree to abide by these conditions as stated in the Patient Information Sheet.	
15.	Based on the above information, I voluntarily agree to take part in this research study.	

CONSENT FOR STUDY PARTICIPATION			
Name of Patient:	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
Name of person taking consent (if different from Investigator)	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
Name of Investigator	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)

OPTIONAL CONSENT FOR FUTURE EXPLORATORY RESEARCH **I agree to the future exploratory research which may be conducted by the Sponsor using the blood and urine samples collected from me during this study and understand that this will be undertaken within the study sample storage period.**			
Name of Patient:	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)

Name of Investigator	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
CONSENT FOR GENETIC ANALYSIS **I give consent for the collection of the blood sample for the purposes of future genetic analysis as required by the study Sponsor as indicated by my signature below.**			
Name of Patient:	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
Name of Investigator	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)

When completed,

1 (signed counterpart) for patient;
1 (signed counterpart) for study doctor's site file
1 (original) to be kept in the patient's medical notes