SIMBEC-ORION

Simplified Title: A study to investigate the safety, tolerability and activity of multiple ascending doses of DNDI-0690 in healthy volunteers including assessment of heart and kidney function.

Study Number: RD777.34920 (DNDi-0690-02)

STUDY PART C - PARTICIPANT INFORMATION SHEET – Part 1

1. INVITATION PARAGRAPH:

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.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you want to take part.

You will be asked to sign a form to confirm your consent to take part and that you understand the information provided to you. This participant information sheet is for **Part C of the study only.**

Thank you for reading this.

2. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to investigate the study drug DNDI-0690.

The main objectives of this study are as follows:

- To determine the safety and tolerability (degree to which side effects of a drug can be tolerated) of DNDI-0690 when it is administered as multiple doses at different dose strengths over a period of up to 10 days.

- To investigate the concentration of DNDI-0690 in the blood and urine, how this changes over a period of time and whether there are differences in the concentration profile between different dose strengths.

- To investigate whether DNDI-0690 has any effect on the function of the heart and kidneys.

As well as evaluating the above, we will also investigate, as exploratory objectives, the profile of by-products of DNDI-0690 (known as metabolites) which are produced when DNDI-0690 is broken down in the body, and analyse the levels of 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 also assess variations in the levels of certain molecules in the body before and after exposure to the study drug. This will be performed by analysing a certain molecule in your body called mRNA (messenger RNA) which is responsible for producing the genetic code which makes proteins in the body. This investigation will apply to certain groups only.

This study will be split into 3 separate parts: Part A, Part B and Part C. Each study part will assess a different combination of the study objectives.

The purpose of Part A is to evaluate the safety, tolerability and concentration of DNDI-0690 in the blood and urine when it is given at different dose strengths, once or twice a

day, for 10 days. Part A will consist of up to 4 groups of 9 participants; each group investigating a different dose strength.

The purpose of Part B is to evaluate the safety, tolerability and concentration of DNDI-0690 in the blood and urine when it is given once a day for 5 days at a maximum dose strength of 3600 milligrams (mg) and to evaluate the effect of this dose on the function of the heart. Part B will consist of 1 group of 9 participants investigating a dose strength higher than that which is intended to be given in order to treat the disease. This part of the study is considered optional.

The main purpose of Part C is to evaluate the effect of DNDI-0690 on the function of the kidneys when it is given once a day for a period of 10 days. In addition to this, Part C will also evaluate the safety, tolerability and concentration of DNDI-0690 in the blood and urine when it is given once a day for 10 days. Part C will consist of 1 group of 9 participants investigating a dose strength considered to be the highest well tolerated dose strength from doses investigated in Part A. In Part C, we will measure the effect of DNDI-0690 on kidney function by giving participants an injection of a chemical called iohexol before they are given the study drug and after they have taken the drug for a period of 10 days. Iohexol is a solution which is used in imaging such as X-rays and CT scans that enhances images of the veins, arteries, parts of the brain and other tissues such as the joints. This solution is easily filtered by the kidneys and so the purpose of giving this injection is to measure whether DNDI-0690 has any effect on kidney function by measuring the levels of iohexol in the blood and urine and how these compare before and after taking the study drug. The injection which will be given in this study is a very small dose compared to the dose which is used in the types of imaging procedures described above.

In this study, participants will either be given DNDI-0690 in the form of an oral capsule (multiple capsules per dose) or a placebo (which contains no active drug).

Blood and urine samples will be taken at set time points throughout the study in order to measure the concentration profile of DNDI-0690 in the blood and urine, how this changes over time and for the monitoring of heart and kidney function. We will compare the results from each of the groups and each study part to determine if there are any significant differences in the safety profile of DNDI-0690, the concentration of DNDI-0690 in the blood and urine and how this changes over time or the effect on heart and kidney function.
The purpose of the data generated in this study is to provide further information and guidance to support the study sponsor in development of the study drug. Further information about DNDI-0690 may be found in Section 7.

The study sponsor (Drugs for Neglected Diseases initiative (DNDi)) is developing DNDI-0690 for the treatment of a disease called leishmaniasis. This disease is caused by a parasite (an organism which lives on or in another organism and uses the host to survive) which infects the body of female sandflies. These types of fly bite humans, and this causes the parasite to be passed on and infect a human host.

This disease is commonly found in countries which are less developed with high rates of poverty, malnutrition and poor housing conditions. There are 3 main forms of the disease which can cause symptoms ranging from simple ulcer(s) in the skin, lesions affecting tissues in the mouth, nose and throat to the more complicated form presenting with fever, anaemia, weakness and weight loss which can be fatal if left untreated.

Currently, there are treatment options available for this disease, but these are not the most effective as they require a long duration of treatment, most of them are given as injection (in the muscle or veins), are associated with a number of side effects and are generally not effective against all forms of the disease. Therefore, there is an unmet need to develop potential new treatments with oral therapies which could be more effective, and which could be used to combat all forms of leishmaniasis in the areas affected by the disease.

DNDI-0690 has been given to humans in one previous clinical study and has not been associated with any major side effects (more details are provided in Section 9). This is the first study which will investigate multiple doses of DNDI-0690. DNDI-0690 is being developed by the sponsor DNDi, based in Geneva, 15 Chemin Louis Dunant, 1202, Switzerland. For

more information, you can visit the following website: https://dndi.org/

3. WHY HAVE I BEEN INVITED?

A total of up to 54 participants are needed for this study.

For Part C: a total of 9 participants will be required. In Part C, 6 participants will receive a dose of the active drug DNDI-0690 and the remaining 3 will receive a matching placebo. The dose given in Part C will be selected based on one of the doses which has been investigated in Part A of the study which is considered to be the highest well tolerated dose i.e. the highest dose for which 'side effects' were well tolerated by the participants and that is likely to have the best effect.

All participants must comply with the study entry and exclusion criteria. The most important entry criteria are:

* You are a healthy male or female (of non-childbearing potential i.e. permanently sterilised or post-menopausal) between 18 and 55 years of age.
* You are not taking any medication. If you do take medication, please inform the study doctor as you still may be able to take part in the study if the medication you are taking will not interfere with the study drug.
* You are a non-smoker who has not smoked for at least 12 months prior to the screening visit and you have not used any nicotine replacement therapies such as gums, patches or e-cigarettes within the last 12 months.
* You do not consume more than 6 cups of coffee or equivalent per day.

In addition to the criteria above, you will be provided with a separate participant restriction handbook which details all of the key restrictions which you will need to comply with throughout the study.

We believe you may be eligible to enter the study and are therefore inviting you to take part.

4. DO I HAVE TO TAKE PART?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason.

5. WHAT WILL HAPPEN TO ME IF I TAKE PART?

Part C of the study is a randomised, double-blind study.

In Part C, there will be one group of 9 participants who will take a dose of DNDI-0690 or placebo once a day for a period of 10 days. As described, the dose chosen for Part C will be based on one of the doses investigated in Part A which is considered to be the highest most well tolerated dose.

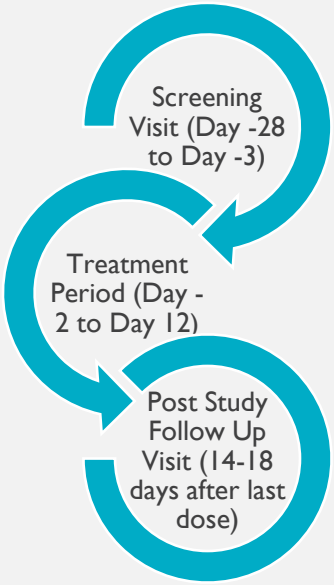
In addition, within Part C, you will be also be given an injection of a solution called iohexol on Day -1 and Day 10 with the option of an additional injection at the post study follow up visit if required.

Iohexol is a solution which is used in imaging such as X-rays and CT scans that enhances images of the veins, arteries, parts of the brain and other tissues such as the joints. This solution is easily filtered by your kidneys and so the purpose of giving this injection is to measure whether DNDI-0690 has any effect on your kidney function. Further information on this can be found later in this document.

Note: You will be informed before your first dose as to which is the chosen dose strength for this part of the study.

Your participation in the trial will last for about 8 weeks (from first screening visit to final study visit).

Part C of the study will proceed as follows:



The key terms of the study are described below:

Randomised Trial: This means that within the study and within the study group you are participating in, you will be randomly allocated to either receive the study drug or a placebo (which contains no active study drug). Within each group, you have a 66% chance of receiving the active study drug (2 in 3).

Double Blind: This means that neither you nor the study doctor 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.

The next section will describe each visit in detail.

Screening Visit (takes place within 28 days of the planned first dose -*you are currently at this visit)*

If you decide to take part in the study, screening tests will be performed to decide if you are eligible. This visit will take place at Simbec-Orion Clinical Pharmacology Unit in Merthyr Tydfil.

You should have fasted for a minimum of 10 hours prior to attending this visit. The following assessments/tests will be performed:

* You will be expected to read through this document (known as the participant information sheet) and if you are happy to do so, you'll be required to provide your signature at the end. Your signature will be asked for under the supervision of a study doctor.
* Once consent has been taken, we will perform a review of the inclusion and exclusion criteria for the study with you to determine if you are eligible.
* A record of your age, gender, ethnicity, date 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 which you are taking or have taken in the past and any relevant injuries or illnesses.
* Blood and urine samples for laboratory safety tests will be taken; HIV and hepatitis will also be tested for. More information can be found at the end of this document.
* The blood sample will be used to measure how well your blood is clotting and if you are a post-menopausal female, we will use the blood 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, marijuana etc), alcohol and cotinine (to confirm that you are not a smoker).
* A measure of your vital signs (blood pressure, heart rate, and temperature).
* A full physical examination by one of the study doctors to confirm that you are in good health. This will include an assessment of your veins to confirm that you are suitable for multiple blood samples during the study.
* An ECG (a recording of the electrical activity of your heart). You will be required to remain in resting position for 5 minutes before the ECG.
* We will check The Over Volunteering Prevention System (TOPS) database to ensure that you have not registered as a volunteer with another clinical trial unit. TOPS is a database that aims to prevent healthy volunteers from taking part too often in trials of new medicines, for their own safety). You will not be able to take part in this study if you are:
* (1) Currently participating in a trial.
* (2) You have participated in a clinical trial of a new un-marketed medicinal product within the last 3 months.
* (3) You have participated in a trial of a marketed drug in the last 30 days.
* (4) If Simbec-Orion Clinical Pharmacology staff have any concerns about you taking part in too many clinical trials.

The above tests and assessments will determine whether you are suitable for participation in this study. You will be given as much time as required to ensure that you fully understand what is involved in the participation of this study.

If you consent to be involved in this study, you must be willing to cooperate with the Investigator and the study restrictions (detailed in the participant restriction handbook) and agree to use the contraceptive methods if you are male described

in Section 10 from the first dose until 3 months after the last dose of DNDI-0690.

Study Visits

Treatment Period – Day -2 to Day 12

If all of your screening assessments are satisfactory, you will be asked to attend Simbec-Orion Clinical Pharmacology Unit (in Merthyr Tydfil) the morning 2 days before dosing (Day -2) for the baseline tests. When you arrive at Simbec-Orion Clinical Pharmacology Unit, we will need to perform a bag search to check for any items such as medication, food and drinks which are not allowed during the study. Additionally, you should note that there are CCTV cameras in operation in various locations in the Clinical Unit. These cameras are signposted, and they provide 24/7 monitoring, for your safety.

You will be required to fast for a minimum of 10 hours prior to attending on Day -2 and the following procedures will be performed:

* A nose and/or mouth swab will be taken in order to detect the presence of any COVID-19 infection. If this result comes back positive, then you will be withdrawn from the study and required to observe the necessary period of self-isolation as per the current UK/Welsh Government guidance. More information on this can be found at the end of this document. Once the results of this testing are known, we will then proceed with the remainder of the Day -2 procedures (provided that your test is negative).
* A check to confirm you are still eligible to take part in the study including a review of the inclusion and exclusion criteria.
* A review of any changes in your medical history, medication which you may have taken since your screening visit and any relevant illnesses or injury etc.
* An assessment of your veins.
* Urine sampling for drugs of abuse, alcohol and cotinine.
* Blood and urine samples for laboratory safety tests including measuring how well your blood is clotting.
* A separate blood sample will also be taken to measure your levels of Troponin I. This is a protein which if found in high levels in the blood can indicate that there is damage to the heart muscle.
* A physical examination to check for any changes in your health since the screening visit. This will be a shortened physical exam compared to the one at the screening visit.
* An ECG (a recording of the electrical activity of your heart).
* A measure of your vital signs (blood pressure, heart rate and temperature).

Once these assessments are complete, you will need to remain overnight at Simbec-Orion Clinical Pharmacology Unit.

Day -1 (Iohexol Administration)

On Day -1, we will perform some assessments to confirm that you are eligible to receive the dose of iohexol.

These will include:

* A physical examination to check for any changes in your health. This will be a shortened exam.
* An ECG (a recording of the electrical activity of your heart).
* A measure of your vital signs (blood pressure, heart rate and temperature).
* A blood sample to measure a baseline level before you are given iohexol.
* A urine sample to measure a baseline level before you are given iohexol.
* A urine sample to measure for biomarkers.

Once these assessments have been completed and it is confirmed that you are okay to do so, you will be given the injection of iohexol.

This will be a single injection of approximately 5 mL. The injection will be given into a vein (known as intravenous or IV injection).

Following the injection, we will take blood and urine samples at set time points to measure the concentration of iohexol in your blood and urine and how this changes over a period of

time. This data will be used to measure how well your kidneys are functioning.

Blood and urine samples will be taken at the following time points: 1 hr, 2 hr, 3 hr, 4 hr and 5 hr after the injection. The urine samples will be pooled which means you will collect all of your urine into a specific container at these time points i.e. from 0-1 hr, 1-2 hr, 2-3 hr and so on.

In addition to these assessments, we will also record any medications which you take and any illnesses/injuries which you report.

You will need to remain overnight at Simbec-Orion Clinical Pharmacology Unit and begin an overnight fast.

DNDI-0690 Dosing (Days 1-10)

On the morning of Day 1, we will perform some assessments to check that you are suitable for dosing. These will include:

* A review of any medication which you have taken overnight or changes in your health status.
* A measure of your vital signs (blood pressure, heart rate and temperature).
* An ECG (a recording of the electrical activity of your heart). This will be taken 3 times, approximately 2-3 minutes apart.
* A blood sample to measure your levels of Troponin I. This is a protein which if found in high levels in the blood can indicate that there is damage to the heart muscle.
* A blood sample to measure a baseline level before you are given the study drug and to measure metabolites.
* A urine sample to measure for biomarkers.
* Blood and urine samples for laboratory safety tests including measuring how well your blood is clotting.

Once these checks have been completed and it is confirmed that you are eligible, we will proceed to dosing. You will be randomly allocated to receive either the active drug DNDI-0690 or a placebo.

On all study dosing days, you will be required to take the dose of the study drug or placebo after an overnight fast of 10 hours.

Doses will be given in the morning and you will be given the drug or placebo in the form of either a 100 mg or 200 mg hard capsule to swallow with 240 mL of water per dose. The number of capsules you take will depend on the dose strength you are taking e.g. for a 400 mg dose, you will either take 4 x 100 mg capsules or 2 x 200 mg capsules as decided by the study team.

Following each dose, you will be required to remain in an upright position i.e. no sleeping or lying down for a period of 4 hours.

In addition, on Day 10 following your DNDI-0690 dose, you will be given a second injection of iohexol as was performed on Day -1.

You will be required to stay overnight at Simbec-Orion from the morning of Day -2 until the morning of Day 12 (total of 13 overnight stays). During this period, we will perform a number of assessments to monitor your safety and to measure the concentration of DNDI-0690 and iohexol in your blood and how this changes over a period of time.

The assessments to be performed on Days 1-10 are as follows:

Table 1

ASSESSMENT	TIME POINT
Vital Signs (blood pressure, heart rate and temperature)	**Day 1:** prior to first dose **Day 4:** prior to first dose **Day 7:** prior to first dose **Day 10:** prior to first dose
Blood samples for determination of drug concentration and metabolites – Pharmacokinetic (PK)	**Days 1, 2, 4 & 7**: prior to first dose **Day 10:** prior to first dose, 30 mins, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 9 hr post-dose
Blood and urine samples for determination of iohexol concentration	**Day 10:** pre-dose, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr after the injection.

	As on Day -1, these will be pooled collections; 0-1 hr, 1-2 hr and so on.
Urine samples for biomarkers	**Day 1, 2, 4, 7 & 10:** prior to first dose
12-lead ECG (recording of heart rhythm)	**Day 1:** prior to first dose, taken 3 times, 4 hr post dose **Day 4:** prior to first dose, 4 hr post dose **Day 7:** prior to first dose, 4 hr post dose **Day 10:** prior to first dose, 4 hr post dose
Blood and urine samples for laboratory safety testing including measurement of blood clotting	**Day 2:** prior to first dose **Day 4:** prior to first dose **Day 7:** prior to first dose **Day 10:** prior to first dose
Blood sample for Troponin I	**Day 1 & Day 10:** prior to first dose
Brief physical examination	**Days 4 & 7:** during study day if required Note: a physical exam may be performed on any study day if the study doctor believes that it is necessary.

We will also ask you to report any side effects that you may be experiencing during this time and document any medication which you take.

Day 11 & Day 12

Following completion of the last dose administration on Day 10, we will continue to perform assessments on Days 11 and 12. These assessments will be as follows:

Table 2

ASSESSMENT	TIME POINT
Vital Signs (blood pressure, heart rate and temperature)	**Day 12:** prior to discharge
Blood samples for determination of drug concentration and metabolites – Pharmacokinetic (PK)	**Day 11:** 24 hr post-dose **Day 12:** 48 hr post-dose
12-lead ECG (recording of heart rhythm)	**Day 12:** prior to discharge
Blood and urine samples for laboratory safety testing including measurement of blood clotting	**Day 12:** prior to discharge
Brief physical examination including weight check	**Day 12:** prior to discharge

Once all of the assessments on Day 12 have been completed (including a side effects and medication check), and the study doctor believes that it is safe to do so, you will be permitted to leave Simbec-Orion.

Post-Study Follow-Up Visit

Approximately 14-18 days after the last dose of DNDI-0690, you will be asked to attend Simbec-Orion for a follow up visit.

Assessments to be performed at this visit will include:

* Blood and urine samples for laboratory safety testing including a measure of how well your blood is clotting.
* A measure of your vital signs (blood pressure, heart rate and temperature).
* A check of any side effects you may be experiencing and any medications which you may have taken since the last visit.

* A brief physical exam to confirm that you are still in good health.
* If required i.e. if your kidney function results following the second iohexol injection are showing abnormalities, you may be required to have a third injection and further blood and urine samples (up to a maximum of 6 additional samples similar to the timepoints on Day 10 as shown in the table above) to confirm that your kidney function has now returned to normal levels.

If following this 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 Simbec-Orion for further follow up visits with one of the study doctors.

MEALTIMES/FASTS

You will be required to fast overnight for at up to 10 hours prior to the first morning dose each day from Days 1-10.

As the study drug is only being given once a day, meals will be served as follows:

- Lunch will be served: approximately 4 h after dose.
- Dinner will be served: approximately 8 h after dose.
- Snack will be served: approximately 12 h after dose.

If the study drug is being given twice per day, meals will be served as follows:

On Days -2, -1, 11 and 12, meals will be served at standard times.

Fluid Restrictions

On each dosing day, you will not be permitted to drink any fluids from 1 hour prior to each dose until 1 hour afterwards (applies to all doses). One glass of water will be given to you to swallow the capsules. However, if extra water is required due to the number of capsules you are required to swallow, this will be given to you.

After this point, you may drink water as freely as you want and should ensure that you drink at least 240 mL every 4 hours whilst you are awake. Squash/cordial are allowed from 4 hours after the first dose on each day and decaffeinated tea and coffee from 8 hours after the first dose on each day.

On the days where you are given iohexol (Day -1 and Day 10), you will be required to drink one glass of water (approximately 240 mL) after each blood/urine sample is taken to measure the concentration of iohexol in your blood and urine i.e. every hour between the injection up to 5 hours after the injection.

6. EXPENSES AND PAYMENT

You will receive a maximum payment of £3950 for the inconvenience of participating in and satisfactorily completing the trial including all return visits and the post study follow up visit.

Terms and conditions related to the payment – Please read carefully:

* Payment **will not** be made until satisfactory completion of all study visits.
* Unscheduled visits may be necessary, you **will not** be paid until these visits are also complete. Although unlikely, sometimes we do need to arrange extra visits to repeat tests etc.
* If you are not compliant with the study schedule, procedures and restrictions, as detailed in this consent form and study restrictions handbook then the payment you receive may be **reduced**. You will be provided with a 'participant restriction handbook' which allows you to quickly refer to the study specific restrictions.
* If you are withdrawn from the study for a medical reason, the payment you will receive will be evaluated by a study doctor. The payment will not be less than pro-rata (pro-rata means a proportional payment which depends on the length of time you have taken part in the study).
* If you choose to withdraw then payment will usually be made on a pro-rata basis unless you have been non-compliant with the study schedule, procedures and restrictions.
* You will not be paid for attending the Screening Visit and attending this visit will not automatically guarantee you a place on the study.
* Occasionally, study dates may change due to unforeseen events. In such a case, we will make every effort to inform you as soon as possible. In the rare circumstance that you have written confirmation that you are eligible

to participate and are due to attend for study participation and the study is withdrawn or study dates are moved, it will be at the discretion of Simbec-Orion and the study Sponsor whether compensation will be provided for this delay.

We strongly advise that you do not spend this payment before you have received it.

Please note, it is the volunteer's responsibility to inform HM Revenue and Customs the payment (regarded as earnings) received for participating in this study. Should an enquiry be made by the Inland Revenue regarding payment from us, Simbec-Orion Clinical Pharmacology would be required to disclose the amount to the inspector. You are advised to keep a record - such as receipts - of any expenses (e.g. travel etc.) which could be offset against tax. In addition, payments received for participating in this study may affect your eligibility for any benefits and welfare payments that you may receive.

Please note that a place on the study cannot be guaranteed. You may be asked to be a **reserve** volunteer. We usually need to have additional volunteers on standby in case of non-attendance, exclusion or a last-minute withdrawal. We cannot always say who will be the reserves prior to the study day itself. We cannot guarantee that you will participate in this study and therefore receive full payment. If we are unable to include you in this study, you will receive a payment which will reflect the inconvenience of the study procedures in which you have been involved (this excludes those performed at screening). However, if you are not included in the study for non-compliance reasons such as a positive drugs of abuse test, alcohol or cigarette use (study admission), **you will not receive any reserve payment.**

Travel expenses

Travelling by Car

If you decide to travel here by car we will reimburse you 20p per mile. Please note, per round trip, a maximum of £50 can be claimed.

Travelling by public transport

Alternatively, you may decide to get here by bus or train please keep the receipts and be sure to show these to the Simbec-Orion Clinical Pharmacology staff in order for your expenses to be calculated appropriately. Please note, per round trip, a maximum of £50, can be claimed.

Please note: All travel expenses will now be made via a BACs payment method, provided an expense claim form has been completed and submitted.

7. WHAT IS THE DRUG BEING TESTED?

In this study, we will be testing a drug called DNDI-0690.

As described in Section 2, DNDI-0690 is being developed for the treatment of a disease called leishmaniasis. There are 3 main forms of the disease: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (ML).

VL is the most fatal form of the disease if left untreated with approximately 95% of cases resulting in death without treatment. Most of the cases of VL occur in Brazil, East Africa and India with an estimated 50,000 to 90,000 new cases each year. VL is associated with symptoms of fever (increased temperature), weight loss, low iron levels (anaemia) and enlargement of the spleen and liver.

CL is the most common form of the disease with an estimated 600,000 to 1,000,000 new cases each year with the majority of cases being reported in South America, the Mediterranean, Middle East and Central Asia. This form is associated with ulceration and lifelong scarring of the skin and exposed parts of the body.

ML is a less common form of the disease with 90% of cases being reported in Bolivia, Brazil, Ethiopia, and Peru. This type is associated with lesions affecting the tissues inside the mouth nose and throat.

Currently there are treatment options available for this disease, but these are not the most effective as they require a long duration of treatment, most of them are given as injection (in the muscle or veins), are associated with a number of side effects and are generally not effective against

all forms of the disease. Therefore, there is an unmet need to develop potential new treatments with oral therapies which could be more effective, and which could be used to combat all forms of leishmaniasis in the areas affected by the disease.

One such development is DNDI-0690. DNDI-0690 is an antiparasitic treatment which is classified as a nitroimidazole. These types of drugs are able to get into the parasite and block the parasite from making proteins which are essential for allowing the parasite to continue making DNA to replicate and grow. By disrupting this process, this causes the parasite to die and stops the spread of the infection.

Previous data for DNDI-0690 suggests that this drug has potential to be a more effective treatment option than those currently available as it has demonstrated high activity in the animal studies, a more favourable safety profile so far but can also be administered via an oral tablet, instead of the painful injections or long infusion in the veins of the current available treatment options.

Data also suggests that this drug could be used for treatment of more than one form of the disease as a combination therapy.

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 leishmaniasis.

8. WHAT ARE THE ALTERNATIVES FOR TREATMENT?

This is a study in healthy volunteers and therefore alternative treatment is not applicable.

9. WHAT ARE THE SIDE EFFECTS OF ANY TREATMENT RECEIVED WHEN TAKING PART AND HOW DO WE DECIDE ON WHICH DOSE TO GIVE?

Like all medications that you take, there can be some side effects associated with taking DNDI-0690.

To date there has been one clinical trial which evaluated DNDI-0690 as single doses in strengths up to 3600 mg in 48 healthy subjects.

A total of 18 adverse events (type of side effects) were reported during this study (importantly, some of these events were reported in the study group who received placebo, and therefore, it cannot be determined if they were caused by the drug or not) The events reported included:

* Headache
* Flatulence (passing gas)
* Loose stools (Diarrhoea)
* Abdominal pain
* Gastroenteritis (inflammation of the stomach and intestine)
* Back pain
* Haematoma in site of vessel puncture (bruising at the site of an injection)
* Fatigue
* Common Cold including inflammation in the nose and throat

It is noted that these side effects were all considered mild to moderate in nature and resolved spontaneously i.e. without any treatment.

As well as a previous clinical trial in humans, there have also been several studies performed in different animal species.

In a study done in monkeys (known as a toxicology study), the test drug (DNDI-0690) has been shown to possibly be harmful to the kidneys. This was observed after 28 days of dosing. The effects in the kidneys observed in the monkeys completely resolved and returned to normal once the study drug was stopped. However, as these studies are designed in order to determine what a toxic dose of the drug would be and therefore the drug is given continuously and not stopped for any reason, we would acknowledge that 2 monkeys died from complications of this toxicity.

In addition, in the previous clinical trial in humans, this effect was not observed, but some markers of the kidney function were slightly altered (creatinine level increase) while others remained normal. In the human study, this alteration was not considered a problem or a safety concern by the study doctors, but, as a precaution, in this study, blood and urine samples will be regularly collected to test for those markers.

Measuring these markers and how they change throughout the study may indicate if there has been any damage to your kidneys and if required, the study may be stopped for you, and no further drug administration may be undertaken.

In the same study in monkeys, changes to liver function after the test drug administration were noted and based on these results, it is thought that some changes to liver function could be anticipated. This was not found in humans after a single dose but as part of this study, we will continue to monitor liver function. Similarly, in the animal studies, there was some toxicity effect on the heart. For that reason, we will monitor your heart closely, with ECG monitoring at regular intervals throughout the study. We will also look at biomarkers in your blood (biomarkers indicate specific processes in the body) which are specific to for heart injury (Troponin I). We will also analyse blood samples to look at other functions of your body in order to monitor the safety of the test medicine. The effects of the study drug in pregnant women is unknown, this is why only females that are no longer able to have children (non-childbearing potential) are included in this study.
The maximum dose planned to be given in this study will result in a maximum blood level of the test drug that is expected to be approximately 2.6 times lower than the doses in the animal studies which resulted in side effects relating to the kidney.

In addition, the groups within Part A of the study have been completed (maximum of 36 participants) and the following effects have been reported to date:

[INSERT AE SUMMARY TABLE FROM PART A GROUP DATA]

How will the dose be selected in Part C?
Following completion of all of the groups in Part A, all the available safety data and the data generated from the blood and urine samples taken to measure the concentration of DNDI-0690 in each group from Part A has been reviewed by your study doctor along with other members of the study team from Simbec-Orion Clinical Pharmacology and the sponsor to confirm there are no safety concerns. A decision will be made as to which is the most appropriate dose to give in Part C which is considered as the highest well tolerated dose from all of the doses investigated in Part A i.e. the highest dose which showed the most acceptable safety profile but which is also likely to have the best therapeutic effect.

You will be informed prior to your first dose as to what dose strength has been chosen for this study part.

Potential side effects and how we minimise the risk?

This is the first study to test DNDI-0690 in multiple doses in humans; therefore, we have limited information on the potential side effects of DNDI-0690.

Therefore, 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.

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.

There is a potential risk of unforeseeable allergic reactions as for any drugs; however, these are 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

Iohexol Side Effects

As the part of the study involves the administration of iohexol, there are also side effects which you should be aware of for this product. This product is a marketed product which is currently available in the US and EU.

The side effects reported for this product when injected in the veins include the following:

Frequency	Side Effect
Common (occurs in 1 to 10 in every 100 people)	- Feeling hot - Change in respiratory rate - Difficulty breathing

Uncommon (occurs in 1 to 10 in every 1000 people)	Feeling cold, - Wet hands or excessive sweating - Fainting - Pain and discomfort at injection site
Rare (occurs in 1 to 10 in every 10,000 people)	- Headache - Vomiting - Diarrhoea - Dizziness - Allergic reactions - Paresis (muscle weakness caused by nerve damage), Paralysis (loss of muscle function in a part or multiple parts of the body) - Eye sensitivity to light - Somnolence (sleepiness or drowsiness) - Changes in heart rhythm - Slowing of heart rate - Disturbances in vision including temporary blindness - Fever/increased temperature - Cough, - Respiratory arrest, - Rashes of the skin - Itching - Urticaria - Fainting - Fatigue - Changes in kidney function - Kidney failure
Very Rare (occurs in less than 1 in every 10,000 people)	- Disturbance in taste including lack of taste - Warmth or redness of the skin - Increases and decreases in blood pressure - Heart attack - Diarrhoea – loose stool - Abdominal pain/discomfort – pain in the stomach - Shivering (chills) - Seizures – electrical disturbances in the brain including fitting - Changes in alertness due to disturbance in the brain - Sensory abnormalities – changes in sensation or touch e.g. pins and needles or tingling - Tremor - uncontrolled/involuntary muscle twitches - Dyspnoea – difficulty breathing
Frequency not known (reported during marketing studies)	- Low levels of platelets - Anaphylactic /anaphylactoid reaction – severe allergic reaction - Fainting/lowered levels of consciousness - Increase in size of glands which produce saliva (spit) - Changes in thyroid function - Confusion, restlessness, agitation and anxiety

	- Severe cardiac complications - Heart attack/heart failure - Short term loss of hearing, sight or movement/speech - Short term memory loss, disorientation & brain swelling - Inflammation or clots in the veins or arteries - Severe respiratory symptoms and signs, lung conditions including fluid on the lungs, difficulty breathing, asthma-type symptoms - Aggravation of pancreatitis, inflammation of the pancreas - Skin conditions including severe rashes or blistering/ulceration of the skin - Pain, weakness or spasm in the muscles or joints - Reactions at the injection site - Iodism – iodine poisoning

You should report any side effects to the clinical staff at Simbec-Orion Clinical Pharmacology. The contact details for the study doctors are:

Simbec-Orion Clinical Pharmacology Doctor Contact Number: 07894 478 942
(Available 24 hours a day, 7 days a week)
Simbec-Orion Clinical Pharmacology Clinical Team Contact Number: 0800 691995
(Available 24 hours a day, 7 days a week)

Further contact details are provided in Section 24 (Part 2).

Please note that all doctors employed by Simbec-Orion Clinical Pharmacology are trained and certified in Advanced Life Support Procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures. Simbec-Orion Clinical Pharmacology also has an agreement with Prince Charles Hospital for referral of volunteers if required following a medical emergency.

10. WHAT ARE THE OTHER POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

Study Procedures:

Blood sampling: A total of approximately 202 mL of blood (approximately ½ of a pint) will be taken from you during this study (dependent on which group you are in). This is less than is removed during a normal blood donation. It is possible that you may feel some discomfort when the blood samples are being taken.

Cannulation

A cannula (small plastic tube) will be placed in your arm using a small needle. This allows us to take several blood samples without the need to insert a needle in your arm each time. This cannula may remain in place for the day. It will usually be taken out before you go to bed at night. 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.

Insurance:

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. 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.

Additional/Repeat Testing:

During the study, there may be occasions where we need to do some repeat testing or take some extra blood samples from you. This may be due to a number of reasons (such as for safety reasons or if a blood sample is not suitable for analysis; for example, if the blood sample clots). For cases of repeat blood samples, the total volume of blood taken will not be more than approximately 7.2 mL and the overall blood volume will not exceed 450 mL.

Any other assessment in the study may be repeated if the study doctor believes that this is required. You will be told if this is required.

COVID-19 Risks

You should also be aware of the risks of exposure to COVID-19. When you attend the clinical unit at each visit, we will ask you to complete a self-declaration form and temperature check to confirm that you are not showing any early signs of COVID-19 infection and that you have not had any contact with individuals who are currently self-isolating or have tested positive.

Additionally, at the clinical unit, you may be asked to wear a facemask during procedures where clinical staff cannot maintain a 2m distance i.e. blood sampling and will note that all beds within the unit are a minimum of 2m apart or where this is not feasible, beds are separated by Perspex screens.

It is noted that if you have an exemption from wearing a face mask, you will not be required to do so.

In any circumstance, to prevent risk of transmission between staff and participants, all staff will be wearing appropriate personal protective equipment i.e. face masks, face shields etc during the course of the study.

You will also be required to observe good hygiene practice and ensure that you regularly thoroughly wash your hands to minimise the risk.

Furthermore, you will be required to have a COVID-19 test on Day -2 of the study. If this test returns a positive result, then you will not be able to participate in the study and will be required to observe the required self-isolation guidance as per the current UK/Welsh Government recommendations.

Harm to the unborn child

For men:

Please share this information with your partner if they are of child-bearing potential:

It is not known if the study medicine will affect sperm or

semen and therefore you must not father a child during this study or for a safety period of at least 3 months following the last dose of DNDI-0690.

If your partner might become pregnant you must use reliable forms of contraception during the trial and for at least 3 months following the last dose of DNDI-0690, e.g.

- Partner using oral contraceptive + condom
- Partner using Intra-uterine device (IUD)+ condom
- Partner diaphragm with spermicide + condom

If your partner becomes pregnant during the study (up to and including the post study follow up visit), you should inform your study doctor immediately. As the risk to your partner and baby is unknown, it is desirable for your partner to agree to medical supervision during her pregnancy and for the baby after it is born. Your study doctor will work with the sponsoring company to organise this. Your partner will be invited to sign a consent form to allow her medical supervision. The sponsor will also request you and your partner's consent to collect confidential information about her health and that of the baby up until the point of delivery and 2 years thereafter for the baby.

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) until at least 3 months following the last dose of DNDI-0690.

In addition, you must not donate sperm until at least 3 months following the last dose of DNDI-0690.

If your partner is already pregnant, you must still use a condom until at least 3 months following the last dose of DNDI-0690.

11. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

Taking part in this study is not expected to provide you with any direct medical benefit. However, the information we get from this study may help improve the treatment of Leishmaniasis.

12. 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 trial. You will not be able to carry on taking DNDI-0690 after the study has finished, even if you get some unexpected benefit from it.

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 (specifically those blood samples used to measure the levels of DNDI-0690 in your blood or the samples taken for biomarker analysis). 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 DNDI-0690. 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, then you will still be able to participate in the study. Section 19 provides full details of what will happen to your samples.

Study data collected will be stored for at least 25 years after the end of the trial by Simbec-Orion Clinical Pharmacology and DNDi, the study sponsor. Details of who may have access to this data and what might happen to this data during this time are provided in Part 2.

13. WHAT IF THERE IS A PROBLEM AND I WISH TO MAKE A COMPLAINT?

Any complaint about the way you have been dealt with during the study or any possible harm you suffer will be addressed.

Please speak to a member of staff or ask to speak to their immediate Supervisor if you have a complaint regarding your treatment or about our facilities during study visits.

The staff member receiving the complaint will attempt to resolve the matter as soon as possible. If the staff member is unable to resolve the complaint, then it will be passed on to their Supervisor to be dealt with.

You are welcome to put your complaint in writing addressing it either to the relevant Head of Department or the Head of Simbec-Orion Clinical Pharmacology. Written complaints should be sent to the following address: Simbec-Orion Clinical Pharmacology, Merthyr Tydfil Industrial Park, Cardiff Road, Merthyr Tydfil, CF48 4DR or via email to enrolmentservices@simbecorion.com.

Alternatively, you may make a verbal complaint by contacting the following number 0800 691 995 and selecting the relevant option for the department that you wish to contact.

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in Part 2 before making any decision.

PART 2

14. WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes during a research project, we receive new information about the study drug being studied. If this happens your research 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 research 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 research doctor may consider it to be in your best interests to stop the study. He/she 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.

15. WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

If you withdraw yourself from the study, you are advised that any data and samples collected up to the point of your last follow up visit will be analysed, reported and provided to the Sponsor unless you request otherwise. As a research participant, you have the right to request that your samples are destroyed if you no longer wish to continue your participation in the study. No further information will be collected after your last follow up visit. Even if you decide to stop taking the drug, for your own safety, you are encouraged to attend the follow up visits as advised by your study doctor.

In the event that you are withdrawn from the study by the research doctor, your data will still be analysed, reported and provided to the Sponsor.

16. WHAT IF THERE IS A PROBLEM AND I WISH TO MAKE AN INSURANCE CLAIM?

Simbec-Orion Clinical Pharmacology and 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.

Simbec-Orion Clinical Pharmacology and the Sponsor will follow the compensation guidelines developed by the Association of British Pharmaceutical Industry (ABPI), the Bioindustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health and National Research Ethics Service. A copy of the insurance and compensation guidelines can be obtained at http://www.abpi.org.uk/ourwork/library/guidelines/Pages/default.aspx (a printed copy can be provided upon request).

If you are not sure about any of the information above, or wish to make a claim, you should contact Simbec-Orion Clinical Pharmacology (details in section 24 of this information sheet). Section 24 also lists contact details for organisations that may be able to help in progressing a possible claim. The organisations may also be able to help in assessing whether a possible claim is well-founded. These organisations are the Association of British Pharmaceutical

Industry (ABPI) and the Clinical Contract Research Association (CCRA).

17. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

All information collected about you during the course of the study will be kept strictly confidential.

If you agree to take part in the research some parts of your medical records held at Simbec-Orion Clinical Pharmacology and the data collected for the study may be seen by the study sponsor, its associated entities, manufacturer of DNDI-0690 and third parties acting on their behalf, for purposes of analysing the results. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

We may be required by law to disclose the results of the study and the data generated from the study may be submitted to the Medicines Regulating Bodies of one or several countries. You will not be referred to by name in any of these reports. If you agree to take part in the study, then your information may be passed on to researchers or regulatory authorities in countries that do not provide the same data protection as the UK. Simbec-Orion Clinical Pharmacology will take all reasonable steps to protect your privacy.

In order to maintain the confidentiality of the study for the Sponsor you will agree to keep all information relating to the conduct of the study confidential.

This study is undertaken according to the ethical guidelines of the Declaration of Helsinki (Brazil, 2013) and complies with the recommendations of the ABPI Guidelines for Phase I Trials (2018) and also complies with local laws, recommendations and guidelines at present in force in the United Kingdom for the investigation of new therapeutic agents. A copy of the Declaration of Helsinki (Brazil, 2013) is available from Simbec-Orion Clinical Pharmacology Enrolment Services Office on request.

By taking part in a clinical trial and signing the consent documents, you are agreeing for personal information to be collected by the Sponsor and their affiliates. Your health information may be used or shared for the purposes of this research study and research related to Leishmaniasis or related diseases, common pathways (links) among diseases, the use of the experimental drug DNDI-0690 in disease therapy, and/or the development of tests or tools that help with detection or understanding of Leishmaniasis. The legal basis for collecting and processing your personal data is the sponsor's legitimate interest to conduct the study to deliver a new treatment for Leishmaniasis and the global interest of improving the health and care of patients affected by this disease. If you accept to participate in this study, the collection and processing of your personal data is necessary.

There are two kinds of information collected about you in this study:

1) your personal data that directly identifies you (e.g. your name, date of birth, address...)

and

2) pseudonymised (encrypted) data, that does not directly identify you because it uses a number code.

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 DNDi, 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 clinical trial. This access to personal data can only occur at the study site (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 the 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 Ethiopia, Sudan, India, the United States of America). However, this data will be protected by corporate rules and binding contracts and will not be able to be traced back to you. Your coded personal data may be used for additional research purposes and may be combined with other databases for such purposes.
If you require information on where your data will be

transferred and under what conditions, please contact your study doctor or Simbec Orion in first instance. In exceptional circumstances where required due to safety concerns or to investigate fraud, your identifying personal data may be disclosed to the sponsor and other individuals authorized by the sponsor (such as the insurance representatives).
If the results of the study are published in a scientific journal, and in the report which will be written about the results of the study, only the encrypted data will be used.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible and in an encrypted manner as mentioned above.

You have the possibility to object to the processing of your personal data, but this will mean that you will have to stop participating in the study. In addition, you have the right to access and correct your data. While we are treating your request, you have the right to ask for suspension of the processing of your data.

The sponsor of this study, DNDi, controls the data for this study and is responsible for their processing.
Every person who has access to your data is subject to national Data Protection laws and to the General Data Protection Regulation (GDPR).

The duration of the storage of your data is regulated by law. Currently, your data will be stored for 25 years after the end of the trial or, if longer, until the end of 2 years after marketing authorisation approval for the study drug.

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

The data processor/Data Protection Officer at Clinical Site:

Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park, Cardiff Road,
Merthyr Tydfil, CF48 4DR
DPO.Team@simbecorion.com

The Data Protection Officer of the Sponsor: The sponsor's Data Protection Officer (DPO) can be contacted at dataprivacy@dndi.org for any general questions during or after the study completion.

As DNDi is based outside the EU/UK, the nominated Data Protection Representative for this study is Mydata - T LTD
Waldeck House, Lyne Lane,
Chertsey, KT16 0AW
UNITED KINGDOM
You also have the right to file a complaint with the Information Commissioner's Office 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

Additionally, you should note that there are CCTV cameras in operation in various locations in the Clinical Unit. These cameras are signposted, and they provide 24/7 monitoring, for your safety. The video footage recorded within this system will be stored for a period of 1 month from capture; after which point, it will be destroyed.

18. 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.

19. WHAT WILL HAPPEN TO ANY SAMPLES/DATA I GIVE?

When your samples and data are stored at the Simbec-Orion Clinical Pharmacology site in Merthyr Tydfil, they will be stored and handled as described below.

Your name will not be included on any of your samples and your medical confidentiality will be respected.

All blood and urine samples for laboratory safety testing will be measured on site by Simbec-Orion Laboratory Services or by a qualified laboratory sub-contracted by Simbec-Orion (e.g. a local hospital laboratory). These samples will be kept

for up to approximately 3 months, after which they will be destroyed.

The blood and urine samples which are taken to determine the concentration of DNDI-0690 and its' metabolites and and urine samples for exploratory biomarkers will be processed on site at Simbec-Orion Clinical Pharmacology and transported for analysis at a laboratory based in Belgium called SGS Life Sciences Laboratories.

These samples (which do not contain any material which could identify you as an individual i.e. DNA) will be analysed and stored for a period of up to 1 year by the sponsor after the clinical study report for the study and main analysis has been finalised and completed.

These samples will be coded with a unique identifier with no personal information included which could identify you as an individual. Equally, these samples themselves do not contain any material such as DNA which could be analysed and identify you as an individual as they have been processed to remove any cells which may contain DNA.

The samples taken to measure the concentration of iohexol in your blood and urine will be processed on site at Simbec-Orion Clinical Pharmacology and transported for analysis at a suitably qualified laboratory chosen by the study sponsor to conduct this analysis. These samples (which do not contain any material which could identify you as an individual i.e. DNA) will be analysed and stored for a period of up to 1 year by the sponsor after the clinical study report for the study and main analysis has been finalised and completed.

These samples will be coded with a unique identifier with no personal information included which could identify you as an individual. Equally, these samples themselves do not contain any material such as DNA which could be analysed and identify you as an individual as they have been processed to remove any cells which may contain DNA.

OPTIONAL FUTURE RESEARCH

Once the main analysis on the samples has been completed, the sponsor may wish to conduct further exploratory research to support the future development of DNDI-0690 using the samples collected during this study. 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 1-year storage period.

This exploratory analysis may take place at a suitably qualified laboratory chosen by the study sponsor and will be undertaken during the storage period where they will be held by the study sponsor.

You will be informed if testing on your samples for this study will change.

20. WILL ANY GENETIC TESTS BE DONE?

There is no genetic testing planned in this part of the study.

21. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

Your data will be analysed by Simbec-Orion Clinical Pharmacology, DNDi or other companies acting on behalf of DNDi to see how the drug has worked in you and the other people in the study. 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 volunteers who entered the study. DNDi 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. If you are interested in the overall results of the study, you can contact the study site or your study doctor, and together with the sponsor, they will make all efforts to share the outcome of the study with you in an understandable way.

Section 15 provides details of what will happen to your data if you withdraw from the study.

22. 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 1. This study has also been reviewed and given approval by the Medicines and Healthcare products Regulatory Agency (MHRA), the main UK drug regulatory body.

23. WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study is funded and sponsored by: Drugs for Neglected Diseases initiative (DNDi)

Simbec-Orion Clinical Pharmacology is carrying out the research.

The Chief Investigator for this study is: Dr Ezanul Wahab, Simbec-Orion Clinical Pharmacology.

Simbec-Orion Clinical Pharmacology is a commercial organisation and will be receiving payment for this study.

24. FURTHER INFORMATION AND CONTACT DETAILS

General Information about research:

Volunteers are able to gain independent advice regarding clinical trials from UK Clinical Research Collaboration (UKCRC) at www.ukcrc.org.

Specific information about this research project:

The following persons may be contacted for further information regarding this study:

Chief Investigator: Dr Ezanul Wahab

Project Manager: Dr Lan Tann

Alternatively, you can speak to one of the study doctors working at Simbec-Orion Clinical Pharmacology using the same number below.

Simbec-Orion Clinical Pharmacology Clinical Team Contact Number: 0800 691995
(Available 24 hours a day, 7 days a week)

Who you should contact in case of study concerns/queries:

Please contact one of the study doctors listed above, using the following numbers:

Simbec-Orion Clinical Pharmacology Doctor Contact Number: 07894 478 942
(Available 24 hours a day, 7 days a week)

Simbec-Orion Clinical Pharmacology Clinical Team Contact Number: 0800 691995
(Available 24 hours a day, 7 days a week)

Who you should contact in the event of a Serious Medical Emergency:

In the event of a serious medical emergency please **call 999** and request immediate medical attention. After the medical emergency has resolved please contact one of the study doctors listed above.

Examples of study related concerns and serious medical emergencies are listed below:

Study related concerns*
Possible allergic reaction to study drug. For example, a skin rash.
Unable to attend a follow up/return visits.
Seek advice about using other medication/ Inform doctor about use of other medication. (Remember, use of other medication is not advised, as detailed in the study restrictions handbook).
You feel unwell, but you are conscious, able to talk, breathing is normal and show no signs of circulatory problems.
You have breached one of the study restrictions – e.g. Consumed alcohol (Study restrictions detailed in study restrictions handbook
Update the study doctor to say you have been hospitalised and/or require surgery.

Serious medical emergency*
Severe difficulty breathing
Chest pain
Fracture/s

*Please note this list is not exhaustive but should help you distinguish whether to call a Simbec-Orion Clinical Pharmacology study doctor or the emergency services.

If you decide to take part in the study you will be provided with a contact card with the telephone number of Simbec-Orion Clinical Pharmacology.

Who you should contact for information about how to make an insurance claim:

Information about how to make a claim and where to seek further information or assistance in progressing a claim can be found from one of the following industry associations:

ABPI (www.abpi.org.uk).

CCRA (Clinical Contract Research Association, www.ccra.org.uk).

If you decide to take part in the study you will be given a copy of your signed consent form and this information sheet to keep

CONSENT FORM

Simplified Title: A study to investigate the safety, tolerability and activity of multiple ascending doses of DNDI-0690 in healthy volunteers including assessment of heart and kidney function.

Study Number: RD777.34920 (DNDi-0690-02)

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), 15 Chemin Louis-Dunant, Geneva, Switzerland

Simbec-Orion Clinical Pharmacology ID Number					
Screening Number:					
Subject Initials					
Date of Birth (DD/MMM/YY):	____ ____ / ____ ____ ____ / ____ ____				

NAME OF CHIEF INVESTIGATOR: Dr Ezanul Wahab

The following consent form will be signed by the participant to confirm consent:		
		Please initial
1.	I confirm that I have read and understood the information sheet dated 14 December 2020 (Version: v3.0) for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	
2.	I confirm that I have read and understood the participant restriction handbook dated 29 September 2020 (Version: v1.0) for this study and agree to abide by the restrictions detailed within the handbook throughout the study.	
3.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4.	I am willing to allow my GP to be informed of my participation in the study and agree that any relevant medical findings will be referred to my GP.	
5.	I understand that sections of any of my medical notes may be looked at by responsible individuals from Simbec-Orion Clinical Pharmacology, the study sponsor or from regulatory authorities where it is relevant to my taking part in research. I give permission for those individuals to have access to my records. I agree that data about me relating to this study may be sent to countries that do not have data protection laws similar to those in the UK.	
6.	I agree to take part in the above study and to abide by the conditions stated in the Participant Information Sheet.	
7.	I agree that the blood and urine samples I donate as part of this study will be stored and analysed as detailed in section 19. I also understand that I have the right to have my samples destroyed at any time during the study at my request if I choose to withdraw from the study.	

8.	I agree that, if I have a confirmed positive result for HIV antibody, Hepatitis B or C, I will be referred to a Department of Genito-Urinary Medicine/Gastroenterology clinic for further investigations, counselling and treatment as necessary and my GP will be informed of the result.	
9.	**OPTIONAL:** I agree to the future exploratory research which may be conducted by the sponsor using the samples collected from me during this study and understand that this will be undertaken within the study sample storage period.	
10.	I understand the purposes and the way the information concerning me collected during the trial will be used in the UK and abroad. I don't object to such processing and further use of the information for research purposes. I agree that data about me relating to this study may be sent to countries that do not have data protection laws similar to those in the UK. I understand that if I withdraw my consent to participate in this study, DNDi will keep any samples or data collected up to the point of my withdrawal.	
11.	I give consent for the COVID-19 testing to be performed in this study. I understand the risks associated with the procedure, the limitations of the testing and the implications of any test result I may receive.	

1. CONSENT FOR STUDY PARTICIPATION			
Name of Participant:	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
Name of Investigator	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)

2. OPTIONAL CONSENT FOR FUTURE RESEARCH & FUTURE ANALYSIS OF SAMPLES (only to be signed if participant agrees to consent line 9)			
Name of Participant:	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)
Name of Investigator	Signature	Date (dd/mmm/yyyy)	Time (hh:mm)

I confirm that I am happy to receive an electronic copy of this Consent Form and Information Sheet via email.		
Name of Participant:	Signature	Date (dd/mmm/yyyy)
SIMBEC-ORION STAFF ONLY Consent Form Quality Control performed by:	Signature	Date (dd/mmm/yyyy)

INFORMATION SHEET FOR HIV ANTIBODY, HEPATITIS B & C TESTING

Simplified Title: A study to investigate the safety, tolerability and activity of multiple ascending doses of DNDI-0690 in healthy volunteers including assessment of heart and kidney function.

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1. INTRODUCTION

HIV ANTIBODY TEST: is a test currently being used to determine if someone may have been infected with HIV. The test does not tell if you have HIV or if you will get AIDS. It takes 4 to 6 weeks or longer from exposure to HIV to positive results in the blood. A positive test result should be confirmed by further testing. The sample will be sent to the Public Health Laboratory in the University Hospital of Wales for further testing. The Public Health Laboratory may store your sample for up to 2 years.
The sponsor of this study requests that this test will be run on all subjects wishing to participate in the study, and Simbec-Orion Clinical Pharmacology is required to perform this test.

You will receive counselling by a physician before you take the test. The physician will explain to you the possible consequences of taking the test and prepare you for the results of the test. The test will be explained to you in the context of this research study.

HEPATITIS B & C TESTING: are standard safety tests for the presence of the Hepatitis B and C viruses or antibodies in your blood. This test is carried out for both your benefit and for the safety of the clinical and laboratory staff that routinely handle and process blood samples. Hepatitis B & C are transmitted in much the same way as HIV.

2. PROCEDURE

HIV ANTIBODY TEST: If your test result to the HIV antibody test is negative and all other laboratory test requirements are within the range as required by the study, you will qualify for entry into the study. The test results will become part of your study file.
If your result to the HIV antibody test at Simbec-Orion Clinical Pharmacology is positive, a blood sample will be sent to an independent laboratory in order to confirm the result. At this stage, only if your result is confirmed as being positive will you be called to the clinical pharmacology unit (CPU), at Simbec-Orion Clinical Pharmacology and informed of a positive result. If your test result to the HIV antibody is confirmed as positive, your laboratory results will be given to you or destroyed. If your test result is positive, you will not be allowed to enter the study.

If your result is confirmed as positive, Simbec-Orion Clinical Pharmacology will also refer you, to the Department of Genito-Urinary Medicine (GUM clinic or sexual health clinic) for further investigations, counselling and treatment as necessary. This clinic operates on a code which assures your confidentiality. Simbec-Orion Clinical Pharmacology cannot be held responsible for any further testing or treatment. We will also inform your GP of the result.

Taking the HIV test will not in any way affect your ability to obtain insurance and / or a mortgage or other services. However, it must be emphasised that, while you are waiting for the results of an HIV test, or if you have a positive HIV test result, your ability to obtain life insurance, health insurance, a mortgage, employment and other services, could be adversely affected.

HEPATITIS B & C TESTS: If your result to any of the Hepatitis B & C tests is positive, we will recall you for a repeat test to confirm your Hepatitis status. If the repeat test is also positive then Simbec-Orion Clinical Pharmacology will then refer you to the local specialist who will then be responsible for your future care. If your test result is positive, you will not be allowed to enter the study.

INFORMATION SHEET FOR COVID-19 PCR TESTING

Simplified Title: A study to investigate the safety, tolerability and activity of multiple ascending doses of DNDI-0690 in healthy volunteers including assessment of heart and kidney function.

Study Number: RD777.34920 (DNDi-0690-02)

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), 15 Chemin Louis-Dunant, Geneva, Switzerland

1. INTRODUCTION

As one of the requirements for participation in this study and in line with the current risk management strategies employed at the Simbec-Orion Clinical Pharmacology Unit in light of the COVID-19 pandemic, you will be required to have a negative COVID-19 test on Day -2 of the study.

The purpose of this test is to detect the presence of an active COVID-19 infection. As detailed earlier on in this document, if this test result comes back positive, then you will be withdrawn from the study and required to observe the necessary periods of self-isolation and associated reporting procedures as per the current Welsh and UK Government guidance.

You should also be aware that if whilst you are at the clinical unit, you begin showing symptoms of COVID-19, you will be required to have a second test to confirm as to whether you have a positive case of COVID-19 and will be subject to isolation procedures within the clinical unit as required by Simbec-Orion standard procedures for management of a suspected positive case of COVID-19.

2. PROCEDURE

In order to test for a current case of COVID-19, we will take a swab from the back of your nose or throat.

The nasal/throat swab testing will provide a result which will determine whether you are currently testing positive for COVID-19; this is known as a Polymerase Chain Reaction (PCR) test. A PCR test detects the presence of COVID-19 genetic material. This type of genetic material shows the virus is currently active/multiplying in your body. The presence of the virus genetic material in the body is a key indicator as to whether you currently have the COVID-19 infection. It does not give information on an infection you could have suffered from in the past.

The sample will be obtained by a trained member of Simbec-Orion staff. You may feel some mild discomfort or irritation whilst the swab is being taken and this could make you cough; however, this will resolve once the swab has been completed. All staff obtaining samples will be supplied with appropriate personal protective equipment (PPE) to minimise any risks.

Your samples will be analysed in a pseudonymised form using only the subject/screening number assigned to you during the study or your unique Simbec-Orion database ID number (dependent on the circumstances of testing) and your year of birth and will contain no information which could identify you as an individual. The results will also be notified to Public Health Wales (particularly a positive PCR test) to support the collection of daily COVID-19 data. Results will be notified in a pseudonymised manner and will contain no data which could identify you as an individual.

As with most diagnostic testing, there is always a possibility of false positives or false negatives. The possibility of these outcomes is defined by the sensitivity and specificity of the diagnostic tests. The sensitivity of a diagnostic test will tell you the percentage of the proportion of people who test positive out of the population who should have tested positive. For example, if the sensitivity of a diagnostic test is 98%, this would mean that out of 100 people tested who should test positive, 2 of these people would test negative.

The specificity of a diagnostic test will tell you as a percentage the proportion of people in a population who test negative out of the population who should have tested negative. For example, if the specificity of a diagnostic test is 99.8%, this would tell us that 2 out of 1000 people produce a false positive result when they should have tested negative.

The higher the sensitivity and specificity of a test, the more reliable the results. Simbec-Orion intends to use the following testing methods for COVID-19:

Method	Type of Test	Type of Sample	Sensitivity	Specificity
Menarini's Rapid Point of Care Test PCR (SARS-CoV-2 Assay, CE marked)	PCR (confirms current infection)	Nasal Swab	95%	100%
PCR performed 3rd party with The Doctor's Lab (TDL)	PCR (confirms current infection)	Nasal Swab	98%	100%

As you can see, the testing above carries some potential for a false negative result. However, although the sensitivity and specificity of a test can give an indicator of the risk of a false positive/negative in the general population, this is not a clear way to determine the risk of false positive/negative on an individual result.

Based on the sensitivities and specificities for the testing above, it could be estimated that for each individual, the risk of a false negative test may be between 2-4% and so you should be aware of this risk and the implications of a false negative.

False negative testing for COVID-19 could have significant impact as you could unknowingly transmit COVID-19 to those who you come into immediate contact with.

On the basis of this, it is therefore advised that regardless of the outcome of your testing and despite the small risk of false negatives, you should continue to observe and practice the relevant UK and Welsh Government guidelines which have been put in place in order to minimise the risk and spread of transmission of COVID-19.