SIMBEC-ORION

Simplified Title: A study to investigate the safety, tolerability and activity of CpG ODN D35 in healthy volunteers.

Study Number: RD 777.35000 (DNDi-CpG-01)

IRAS ID: 297265

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), Chemin Camille Vidart, 15, 1202 Geneva, Switzerland

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.

Thank you for reading this.

2. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to investigate the study drug CpG ODN D35.

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 CpG ODN D35 when it is administered as a subcutaneous injection (injection into the tissue layer between the skin and muscle) at different dose strengths on one occasion.
* To investigate the concentration of CpG ODN D35 in the blood, how this changes over a period of time and whether there are differences in the concentration profile between different dose strengths.

As well as evaluating the above, we will also investigate, as exploratory objectives, the effect of CpG ODN D35 on the body (known as pharmacodynamics) and analyse the levels of certain biomarkers in the body. Biomarkers are markers within the body such as a molecule or characteristic which can be used to identify the presence of a particular biological process occurring in the body or a particular disease. 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 molecule in your body called mRNA (messenger RNA) which is responsible for producing the genetic code which makes proteins in the body. Furthermore, as this study drug is associated with effects on the immune system, we will assess any potential risks of reactions within the immune system and in particular, the potential risk of a condition called cytokine release syndrome. Further information about this may be found in Section 9 of this document.

The study will consist of up to 4 groups of 8 participants: each group investigating a different dose strength.

In this study, participants will either be given CpG ODN D35 or a placebo (which contains no active drug). Both CpG ODN D35 and the placebo will be administered in the form of one or more subcutaneous injections (injection into the fatty tissue layer between the skin and muscle). All participants in a given group will be injected with the same volume of drug/placebo in the injection and receive the same number of injections. The number of injections to be given

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will vary dependent on the dose strength which is being given in the group.

Blood samples will be taken at set time points throughout the study in order to measure the concentration profile of CpG ODN D35 in the blood, how this changes over time and how this compares with the placebo and at each dose strength.

We will compare the results from each of the groups to determine if there are any significant differences in the safety profile of CpG ODN D35, the concentration of CpG ODN D35 in the blood, how this changes over time and whether there are any differences in these parameters at different dose strengths and in comparison with the placebo.

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 CpG ODN D35 may be found in Section 7.

The study sponsor (Drugs for Neglected Diseases initiative (DNDi)) is developing CpG ODN D35 for the treatment of a disease called cutaneous leishmaniasis (CL). 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 which can cause disfiguration and deformities in physical appearance leading to severe social stigma.

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 injections (in the muscle or veins), are associated with a number of side effects and are generally not effective against all forms of the disease. One oral drug exists but it is associated with a risk of defects in babies who are born whilst the mother is taking the drug so it is difficult to use to treat women who are pregnant. Therefore, there is an unmet need to develop potential new treatments which could be more effective, and which could be used to combat all forms of cutaneous leishmaniasis in the areas affected by the disease. More information about CpG ODN D35 can be found in Section 7 of this document.

This study will be the first study in which CpG ODN D35 has been tested in humans, 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 (more details are provided in Section 9).

CpG ODN D35 is being developed by the sponsor DNDi, based in Geneva, Chemin Camille Vidart, 15, 1202, Switzerland. For more information, you can visit the following website: https://dndi.org/.

3. WHY HAVE I BEEN INVITED?

A total of 32 planned participants are needed for this study. In the study, participants will be split into 4 groups of 8, each evaluating a different dose strength of CpG ODN D35 starting at 7.5 milligrams (mg) in a 0.5 millilitre (mL) injection in Group 1 and increasing up to a maximum of 180mg (12mL as 6 injections) in Group 4.

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

* You are a healthy male between 18 and 50 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 or an ex-smoker who has not smoked for at least 6 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 6 months.
* You do not consume more than 6 cups of coffee or equivalent per day.
* You do not have an individual or family history of any type of autoimmune diseases including (but not limited to) lupus, rheumatoid arthritis, type 1 diabetes or multiple sclerosis (MS), or any history of severe allergy.

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* You have not received a vaccine (including the COVID-19 vaccine) within the last 28 days*.

Note: Receipt of a COVID-19 vaccination during the study is not permitted (from 28 days prior to the dose on Day 1 until 28 days following the dose on Day 1). Therefore, if you are invited to receive your COVID-19 vaccine during this period and still wish to receive your COVID-19 vaccine, you should try to ensure that you receive your vaccine outside of this restriction window. If this is not feasible, then you will be withdrawn from the study and not permitted to participate in the study any further. We will still perform the appropriate post-study follow up assessments on your withdrawal to ensure that it is safe and appropriate to discharge you from the study.

COVID-19 vaccination is currently not recommended during the study because we do not have sufficient information on the test drug to be sure that this will not impact or have any interaction with the vaccination. The test drug (CpG ODN D35) is developed to control the immune response, and similar drugs to this are often used in vaccines as a component in order to make the immune response to a vaccine stronger. It is therefore, highly recommended that you do not receive your COVID-19 vaccination during the defined period described above as we cannot predict the consequences for your safety or on the effect of the COVID-19 vaccination. Further information about this may be found in Section 10.

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. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

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

The study is a double-blind, randomised, placebo-controlled single ascending dose (SAD) study.

The study will be split into 4 different groups with 8 participants in each group; each group will evaluate a different dose strength of CpG ODN D35 starting at 7.5 mg (0.5mL in one injection) in Group 1 and increasing up to 180 mg (12mL in 6 injections) in Group 4. Each group from Group 1 onwards will only take place if it is considered appropriate to do so.

Note: Following completion of each group, safety data and the data calculating the concentration of CpG ODN D35 in the blood will be reviewed by study doctors at Simbec-Orion and the study sponsor to determine whether it is acceptable to move forward and begin dosing of the next study group. Decisions will be made as to whether the planned dose strength for the next group can be given or whether the planned dose should be lowered. In addition, it may be decided that the next dosing group is not required and therefore, it is possible that not all planned groups will complete the study.

You will be informed before your dose if there are any changes with respect to the planned dose (applicable to Groups 2-4 only).

The planned doses for the study are as follows:

Study Group	Product Strength	Number of Injections
Group 1 - 8 participants	Up to 7.5 milligrams (mg) or matching placebo	Single dose administered as a single 0.5 mL injection into the fatty tissue between the skin and muscle
Group 2 - 8 participants	Up to 22.5 milligrams (mg) or matching placebo	Single dose administered as a single 1.5 mL injection into the fatty tissue between the skin and muscle
Group 3 - 8 participants	Up to 67.5 milligrams (mg)	Single dose administered as two or three injections into

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	or matching placebo	the fatty tissue between the skin and muscle for a total volume of 4.5mL
Group 4 - 8 participants	Up to 180 milligrams (mg) or matching placebo	Single dose administered as up to six injections into the fatty tissue between the skin muscle for a total volume of 12 mL

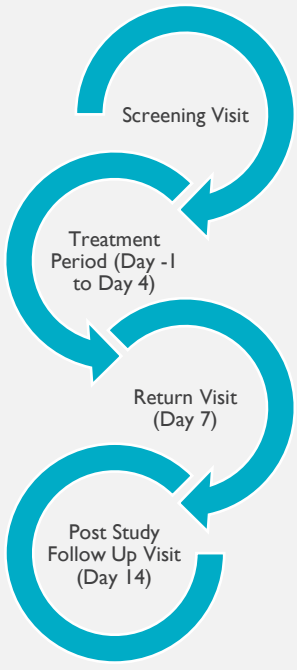
You will note from the table above that the drug may need to be administered as a number of injections, if this is the case, each individual injection will be administered in a different location.

It is also noted that if you are allocated to receive the placebo (containing no active drug), you will receive the same number of injections as volunteers receiving the active drug, according to the study group you are participating in.

You will not know as to whether you are receiving CpG ODN D35 or the placebo as the syringes delivering the injection will be covered prior to administration.

Your participation in the trial will last for about 6 weeks (from first screening visit to final study visit).

The study will proceed as follows:



The key terms of the study are described here:

Randomised Trial: This means that within the study group you are participating in, you will be randomly allocated to either receive the study drug CpG ODN D35 or the placebo (containing no active drug). Within each group, you have a 75% chance of receiving the active study drug i.e., 6 participants in each group of 8.

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), he/she will be able to do so.

Single Ascending Dose: This means that each group will receive single doses increasing in strength per group, on one occasion. As referenced previously, for this study, one dose may consist of several injections.

The next section will describe each visit in detail.

Screening Visit (takes place within 28 days of the planned first dose)

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 **8 hours** prior to attending this visit.

The following assessments/tests will be performed:

* You'll be expected to read through this document (known as the participant information sheet and informed consent form) and if you are happy to do so, you'll be required to provide your signature at the end, on the consent form section. Your signature will be taken 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.
* The study doctor will ask you some questions in relation to your medical history. This will include a review of any medication which you are taking or have taken in the past.

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* A record of your age, gender, ethnicity, height, weight, and body mass index (BMI).
* Blood and urine samples for laboratory safety tests will be taken; HIV, Hepatitis B & C 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 to measure your levels of C-reactive protein (CRP) which is used as a marker of potential infection and inflammation.
* A blood sample will be taken to measure your levels of thyroid stimulating hormone (TSH) to confirm that your thyroid is functioning normally.
* 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, breathing rate and oral temperature). You will be required to remain in a resting position for 10 minutes before the vital signs are taken.
* A full physical examination by one of the study doctors to confirm that you are in good health including an assessment of your veins.
* An electrocardiogram (ECG, a recording of the electrical activity of your heart). You will be required to remain in a resting position for 10 minutes before the ECG.
* We will check The Over Volunteering Prevention System (TOPS) database to ensure that you have not registered as a participant with another clinical trial unit. TOPS is a database that aims to prevent healthy participants 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 described in Section 10 from the dose of CpG ODN D35 on Day 1 until 3 months after the dose of CpG ODN D35 on Day 1.

***PLEASE NOTE:** Any untoward or disrespectful behaviour/language during the pre-screening stage, onsite screening assessment or during the conduct of the study will not be tolerated and will result in volunteers being considered not eligible for participation. Any behaviour of this nature at any point during the study will result in your withdrawal from the study at the discretion of Simbec-Orion in order to protect its staff and the integrity of the study. Any behaviour which is deemed unsuitable may also result in volunteers being removed from the Simbec-Orion healthy volunteer database, and therefore prevent any participation in future studies at Simbec-Orion.

Study Visits

Treatment Period – Day -1 to Day 4

Day -1

If all of your screening assessments are satisfactory, you will be asked to attend Simbec-Orion Clinical Pharmacology Unit (in Merthyr Tydfil) on the morning before dosing (Day -1) 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 **8 hours** prior to attending on Day -1 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

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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, and provided that your test is negative, we will then proceed with the remainder of the Day -1 procedures.

* 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.
* A check of your body weight.
* Urine sampling for drugs of abuse, alcohol and cotinine.
* Blood and urine samples for laboratory safety tests. As part of this testing, the blood sample will be used to measure how well your blood is clotting and to measure your levels of C-reactive protein (CRP).
* A brief physical examination to check for any changes since the screening visit including an assessment of your veins.
* A measure of your vital signs (blood pressure, heart rate, breathing rate and oral temperature). You will be required to remain in a resting position for 10 minutes before the vital signs are taken.
* An electrocardiogram (ECG, a recording of the electrical activity of your heart). You will be required to remain in a resting position for 10 minutes before the ECG.

Once these assessments are complete, you will need to remain overnight at Simbec-Orion Clinical Pharmacology Unit and begin an overnight fast (of at least 8 hours).

Day 1

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

* An eligibility check.
* A review of any medication which you have taken overnight or changes in your health status.
* A brief physical examination to check for any changes in your health including an assessment of the planned site of the injection for dosing.
* A measure of your vital signs (blood pressure, heart rate, breathing rate and oral temperature). You will be required to remain in a resting position for 10 minutes before the vital signs are taken.
* An electrocardiogram (ECG, a recording of the electrical activity of your heart). This assessment will be performed 3 times, approximately 1-2 minutes apart and you will be required to remain in a resting position for 10 minutes before the first ECG and during the exam.
* A blood sample to measure a baseline level before you are given the study drug to be used for the measurement of the concentration of CpG ODN D35 in your blood (pharmacokinetics – PK).
* 2 blood samples to measure a baseline level before you are given the study drug to be used for the measurement of the effect of CpG ODN D35 on your body (pharmacodynamics – PD). This sample will be used for the measurement of markers called cytokines and chemokines. These are proteins which are important in cell signalling and the control of immune responses in the body. As this drug is known to act in the immune system of the body, it is important to monitor how these markers change following exposure to the study drug.
* A blood sample will be taken which will be used to measure the profile of mRNA (messenger RNA) markers. As described previously, mRNA is a molecule which is responsible for producing the genetic code which makes proteins in the body. We will measure these markers at set time points throughout the study to evaluate any impact of the study drug on these markers in the body.
* A blood sample (approx. 40 mL) will be taken to collect a certain type of blood cell (peripheral blood mononuclear cell; PBMC), which will be used to measure other components of your immune system and other exploratory biomarkers.
* A blood sample (approx. 5 mL) will be taken for the purposes of future analysis for the measurement of proteins called autoantibodies. Autoantibodies are proteins produced in the body by the immune system.

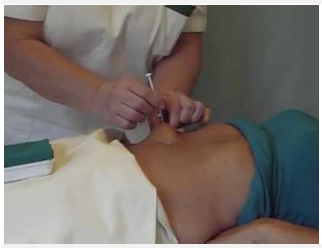
These types of antibodies can be associated with autoimmune diseases such as lupus where the immune system in the body targets parts of the body itself instead of targeting bacteria and viruses etc. in a normal immune response. As this study drug is associated with effects on the immune system and may have the potential to trigger production of autoantibodies, in the event that you would develop any type of autoimmune disease/reaction during or following the study, it would be important to analyse this sample to determine if you had any pre-existing levels of autoantibodies in your blood before you were given the study drug. This would help to indicate as to whether the development of any autoimmune disease/reaction was due to the administration of the study drug or whether you already had existing levels of autoantibodies which may have contributed to the development of this condition. The sample will only be analysed if you develop any indication of autoimmune disease/reaction during or following the study. In all other circumstances, the sample will be destroyed at the end of the sample storage period. Further details of this can be found in Section 19. It is noted that the risk of developing any autoimmune disease following dosing is extremely low; however, as this is the first time that this drug has been given to humans, it is important to evaluate all potential risks, however unlikely the risk is.

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 CpG ODN D35 or placebo. As described previously, 6 participants within each group will receive the CpG ODN D35 and the remaining 2 will receive the placebo.

The dosing group will be split into 3 sub-groups, split into a 2, 3, 3 configuration.

The first 2 participants in each group will be dosed at least 72 hours before the next 2 sub-groups (1 on active CpG ODN D35 and 1 on placebo). Following this 72-hour period, the study doctors will review the safety data from these 2 participants and provided that this data is acceptable, the first sub-group of 3 participants will be dosed. After a further 24-hour period, and following review of the safety data, the final 3 participants will be dosed. This procedure will apply to all of the planned dose strengths in the study.

The drug and placebo will be given via a subcutaneous injection as shown here.



This means a short needle will be used to inject the drug into the fatty tissue layer between the skin and the muscle.

As described previously, depending on the group you participate in, you may need to receive multiple injections per dose in order to administer the correct dose strength. If this is the case, the injections will be administered in different locations. The injections will be administered one after another and you will not know whether you have been given the active drug or the placebo.

You will be required to stay overnight at Simbec-Orion from the morning of Day -1 until the morning of Day 4 (total of 4 overnight stays).

During this period, we will perform a number of assessments to monitor your safety, to measure the concentration of CpG ODN D35 in your blood and to measure specific markers of your immune system including cytokines and chemokines to evaluate the effect of the drug on your body.

The assessments to be performed on Days 1-4 following dosing are as follows:

Table 1

ASSESSMENT	TIME POINT
Vital Signs (blood pressure, breathing rate, heart rate and temperature)	**Day 1:** 15 mins, 30 mins, 1 hr, 2 hr, 4 hr, 8 hr & 12 hr post-dose **Day 2:** 24 hr post-dose **Day 3:** 48 hr post-dose **Day 4:** 72 hr post-dose **Note:** your temperature will be recorded in the morning and evening of each day.
Blood samples for determination of drug concentration – Pharmacokinetic (PK)	**Day 1:** 10 mins, 20 mins, 30 mins, 45 mins, 1 hr, 2 hr & 4 hr post-dose

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Blood samples for determination of effect of CpG ODN D35 on the body (cytokines and chemokines) – Pharmacodynamic (PD)	**Day 1:** 8 hr & 12 hr post-dose **Day 2:** 24 hr post-dose **Day 3:** 48 hr post-dose
Blood sample for mRNA markers	**Day 1:** 4 hr, 8 hr & 12 hr post-dose **Day 2:** 24 hr post-dose **Day 3:** 48 hr post-dose
Blood sample to measure PBMC cells – components of your immune system	**Day 2:** 24 hr post-dose
12-lead ECG (recording of heart rhythm)	**Day 1:** 15 mins, 30 mins, 1 hr & 8 hr post-dose **Day 4:** 72 hr post-dose
Blood and urine samples for laboratory safety testing	**Day 2:** 24 hr post-dose **Day 4:** 72 hr post-dose
Brief Physical examination	**Day 1:** 2 hr, 4 hr & 8 hr post-dose **Day 2:** 24 hr post-dose **Day 4:** 72 hr post-dose
Injection Site Examination*	**Day 1:** 2 hr, 4 hr & 8 hr post- dose **Day 2:** 24 hr post-dose **Day 4:** 72 hr post-dose ***Photographs may be taken of any injection site reactions as required.**

[NOTE: THE TIME POINTS STATED ABOVE ARE SUBJECT TO CHANGE BASED ON EMERGING DATA FROM EACH COHORT. WE WILL AMEND TIMEPOINTS ACCORDINGLY IF NEEDED – MAX BLOOD VOLUME WILL NOT EXCEED 500ML AND STUDY DURATION WILL NOT BE EXTENDED].

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.

Once all of the assessments on Day 4 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.

When you leave you will be given an oral temperature kit and diary card. You will be asked to record your temperature twice a day (morning and evening, approximately 12 hours apart) up to the completion of the post-study follow up visit (may be performed on any day between Day 13-Day 15). For the first recording period, the at-home recording will begin on the evening of Day 4 and finish on the evening of Day 6 .

Note: you do not need to record your temperature on the morning of Day 7 as this will be measured at your return visit to Simbec-Orion.

You will be given clear instructions about using the oral temperature kit and to also make sure you are fully aware of when you should be coming back to Simbec-Orion Clinical Pharmacology for your next return visit.

Within the diary card, you will be provided with specific instructions around symptoms which you should be aware of in relation to a condition called cytokine release syndrome which is a potential risk with administration of CpG ODN D35. More information on this may be found in Section 9 of this document.

If you record any of the symptoms of this syndrome as detailed in the diary, you should contact one of the study doctors immediately using the contact details within the diary. You should ensure that you bring the diary and temperature kit with you to the next visit.

Return Visit (Day 7)

On Day 7, you will be asked to attend Simbec-Orion for a short return visit. As noted above, you should bring your completed temperature diary and kit with you to this visit

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and are not required to take your temperature at home on the morning of Day 7. The purpose of this visit is to perform assessments to monitor your safety and to measure the effect of the drug in your body.

The assessments to be performed at this visit are detailed below:

* A brief physical examination to check for any changes in your health and an assessment of the injection site to check for any reactions. As needed, photographs may be taken of any reactions at the injection site(s).
* A measure of your vital signs (blood pressure, heart rate, breathing rate and oral temperature). You will be required to remain in a resting position for 10 minutes before the vital signs are taken.
* Blood and urine samples for laboratory safety tests. As part of this testing, the blood sample will be used to measure how well your blood is clotting and to measure your levels of C-reactive protein (CRP).
* A blood sample to measure cytokines and chemokines to monitor how these markers have changed following exposure to the study drug.
* A blood sample (approx. 40 mL) to collect a certain type of blood cell (peripheral blood mononuclear cell; PBMC), which will be used to measure other components of your immune system and other exploratory biomarkers.
* A check of any side effects you may be experiencing and any medications which you may have taken since the last visit.

Following completion of these assessments and provided that the study doctor believes that it is okay to do so, you will be permitted to leave Simbec-Orion.

When you leave you will be given a new temperature kit and diary card and should continue to record your temperature twice a day (morning and evening, approximately 12 hours apart). For this recording period, the at-home recording will begin on the evening of Day 7 and finish on the evening of Day 12 or Day 13 (dependent on which day you attend for your post-study follow up visit).

Note: if your post-study visit is on Day 13, you should only record your temperature up to and including the evening of Day 12. If your post-study visit is on Day 14 or Day 15, you should only record your temperature up to and including the evening of Day 13. Further details of this may be found in your diary.

As noted above, you should continue to be aware of any symptoms related to cytokine release syndrome and report these appropriately as per the instructions detailed in your diary.

If you record any of the symptoms of this syndrome as detailed in the diary, you should contact one of the study doctors immediately using the contact details within the diary. You should ensure that you bring the diary and temperature kit with you to the next visit.

Post-Study Follow-Up Visit (Day 13/14/15)

Approximately 13 days after the dose of CpG ODN D35, you will be asked to attend Simbec-Orion for a follow-up visit. As noted above, you should bring your completed temperature diary and kit with you to this visit and are not required to take your temperature at home on the morning of Day 14 (or Day 15 if this is the day of your return visit).

Assessments to be performed at this visit will include:

* A brief physical examination to check for any changes in your health and an assessment of the injection site to check for any reactions. As needed, photographs may be taken of any reactions at the injection sites.
* A weight check.
* A measure of your vital signs (blood pressure, heart rate, breathing rate and oral temperature). You will be required to remain in a resting position for 10 minutes before the vital signs are taken.
* Blood and urine samples for laboratory safety tests. As part of this testing, the blood sample will be used to measure how well your blood is clotting and to measure your levels of C-reactive protein (CRP).
* A blood sample to measure your levels of thyroid stimulating hormone (TSH) to confirm that your thyroid is functioning normally and has not been affected by the study drug.

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* A check of any side effects you may be experiencing and any medications which you may have taken since the last visit.

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

For all groups, you will be required to fast overnight for at least **8 hours** prior to the dose on Day 1.

* Breakfast will be served: approximately 30 mins post-dose.
* Lunch will be served: approximately 4 h post-dose, after completion of all examinations planned at this timepoint.
* Dinner will be served: approximately 8 h post-dose, after completion of all examinations planned at this timepoint.
* Snack will be served: approximately 12 h post-dose, after completion of all examinations planned at this timepoint.

On other non-dosing days (Days 2-4), meals will be served at standard times.

Fluid Restrictions

There are no fluid restrictions to be observed during this study. Other than during the dosing procedure itself, you may drink water as freely as you want. In addition to this, the clinical unit also has squash/cordial and decaffeinated tea and coffee available for consumption.

6. EXPENSES AND PAYMENT

You will receive a maximum inconvenience payment of £1750 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 <u>do not</u> spend this payment before you have received it.

Please note, it is the participant'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.

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Please note that a place on the study cannot be guaranteed. You may be asked to be a **reserve participant**. We usually need to have additional participants 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 CpG ODN D35.

As described in Section 2, this drug is being developed 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.

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 and is caused by over 15 different species of the *Leishmania* parasite.

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.

CpG ODN D35 is specifically being developed for the treatment of cutaneous leishmaniasis (CL) and its complications. Currently there is a limitation to the number of treatment options available for CL and these treatments are often associated with significant side effects including toxicity, difficulty in administration (painful injections) and risk to females who are pregnant (risk of abnormalities in unborn child if the mother takes the drug during pregnancy).

Therefore, there is an unmet need to develop potential new treatments which could be more effective, and which could be associated with less side effects and which can be used in combination with current existing treatments.

One such development is CpG ODN D35. This drug is classed as a Class A CpG Oligodeoxynucleotide Toll-Like Receptor-9 agonist (CpG ODN TLR9 agonist).

Your DNA is the code in your cells which carries all of your genetic information and the instructions for the building of proteins which control all of your functions. This code is made up of a series of blocks called nucleotides which are chemicals that make up your DNA code and are denoted by a series of letters; cytosine (C), adenine (A), guanine (G), and thymine (T).

These letters pair together; C to G and A to T which forms your DNA.

A CpG Oligodeoxynucleotide (CpG ODN) is a short strand of DNA which contains a series of C-G codes that can be detected by TLR9 and acts as a TLR9 agonist.

TLR9 is an important receptor in the immune system which is associated with the control of the inflammatory response in the body, which in turn helps to destroy any pathogen e.g., bacteria, viruses or parasites which may have invaded the body, causing infection and disease. A receptor is a protein which binds to a chemical and initiates response in the body.

An agonist is a substance which is able to bind to a receptor and enhance the effect of the response of the receptor when the chemical binds to the receptor.

In the case of CpG ODN D35, the drug is able to act as an agonist to TLR9 and stimulate/enhance the TLR9 response in the body which in turn increases the production of cells within the immune system which controls the inflammatory response. This inflammatory response corresponds to a stimulation of the immune system cells which can better recognise and destroy the *Leishmania* parasite. This stops the spread of the infection.

Data generated in current animal studies of CpG ODN D35 suggests that this drug has potential to be of added value in combination with currently available treatments as it has demonstrated high activity in the animal studies and a favourable safety profile. It may be suitable for use as a combination treatment with other current approved treatments for CL which are available.

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 participants 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 IN EACH GROUP?

Like all medications that you take, there may be some side effects associated with taking CpG ODN D35.

This is the first study to test CpG ODN D35 in humans and therefore, we have limited information on what the potential side effects of CpG ODN D35 could be in humans.

However, in order for CpG ODN D35 to be considered safe to proceed into testing in humans, there have been a number of studies performed in different animal species (known as non-clinical studies).

These studies concluded that there were no major safety concerns for CpG ODN D35. In these laboratory studies which evaluated doses at higher strengths than are planned to be given in this study, there were no general effects on the body observed which were considered to be related to the study drug. There were some findings which could indicate potential effects and therefore, we will monitor for signs of these effects throughout the study.

One main finding was in relation to reactions at the site of the injection which included bleeding at the injection site as well as inflammation and swelling around the injection site. It was noted that this condition was reversible i.e. the effects resolved naturally without treatment in few weeks.

However, as this phenomenon has been observed and this is the first time that CpG ODN D35 has been tested in humans, we will monitor your injection site(s) throughout the study to document if any effects of this nature are seen. If this type of condition is noted, we will provide advice for management of this as deemed necessary.

Although CpG ODN D35 has not previously been tested in humans, there is some limited data available on the possible effects of this type of drug from other clinical studies in humans of drugs within the same category i.e., Class A ODNs.

In 2 previous studies of other types of Class A ODNs in humans, the following effects were observed:

* Pain, swelling and hardness of the skin around the injection site

* Flu-like symptoms i.e., chills, headache, fatigue and elevated body temperature

These effects were considered mild to moderate in nature and resolved within a few days following administration of the drug.

In addition to Class A ODN studies, there have been more extensive studies carried out with Class B ODNs which act on a different part of the immune system but are generally quite similar in structure to Class A ODNs.

In these studies, the following effects were observed:

* Pain, swelling redness, hardness of the skin, rash and warmth around the injection site
* Flu-like symptoms i.e., chills, headache, fatigue, elevated body temperature, nausea (feeling sick) and vomiting.

These effects were considered mild to moderate in nature and resolved within a few days following administration of the drug. Similar effects could very likely be observed in the present study.

How was the starting dose for the study chosen?

In the first group, a single dose of 7.5 mg (i.e., 0.5 mL injection) of CpG ODN D35 or placebo will be given. This dose has been chosen as the starting dose based on all available data from the laboratory studies conducted with CpG ODN D35. One of the primary goals of this study is to learn about the side effects of giving CpG ODN D35 at different dose levels and to find out the highest dose that can be given without severe side effects. Similar studies were performed in the laboratory in different animal species. The starting dose to be used in this study was chosen based on a dose level tested in animals at which the drug appeared to be well-tolerated and at which no severe side effects were seen.

What happens after each group and how do we decide if it's okay to move onto the next group and which dose to give?

After each dosing group, the safety data and the data generated from the blood samples taken to measure the concentration of CpG ODN D35 in the blood up to 4 hours after the dose on Day 1 in each group will be 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 and a decision will be made whether to proceed with the next group.

Decisions may be made based on the data to determine if changes to the study plan are required. Changes may include choosing a lower dose strength than what is currently proposed or choosing not to proceed with the next dosing group. These decisions will be made based on the data generated in the previous group and if it is not considered appropriate to do so, then the next study group may not proceed.

Potential side effects and how we minimise the risk?

This is the first study to test CpG ODN D35 in humans and therefore, we have limited information on what the potential side effects of CpG ODN D35 could be in humans.

As CpG ODN D35 acts on the immune system, one key potential side effect of these types of drugs is a condition called cytokine release syndrome (CRS).

This is a condition which may occur following administration of drugs which are known to act on the immune system, by modifying the levels of some body messengers called cytokines. Cytokines are proteins which are released into the blood and are important in cell signalling and ensure the control of immune responses in the body. Cytokine release syndrome is caused when there is a large, rapid release of cytokines into the blood from immune cells. The study drug CpG ODN D35, is meant to stimulate the immune cells, and therefore, could trigger some cytokine release. This was not seen in the animal studies but as this could be a severe effect of the drug, we will monitor this throughout the study to ensure your safety.

Signs and symptoms of cytokine release syndrome include fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing. Most individuals with CRS will have a mild reaction, but sometimes, the reaction may be severe or life threatening.

Therefore, throughout the study, we will monitor the levels of cytokines in your blood at set time points and ask you to report to the medical team at Simbec-Orion if you experience any of the side effects mentioned in this section. When you leave the clinical unit on Day 4, you will be given a specific card to keep with you whilst you are outside the clinical unit which will detail the potential early signs of CRS

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and relevant contact details to notify the team at Simbec-Orion who may advise on the most appropriate steps for medical care.

However, if your symptoms worsen or develop, you are advised to seek medical attention from your nearest professional as soon as possible and should notify these professionals that you are taking part in a clinical trial of an oligodeoxynucleotide and provide the contact details for the medical team at Simbec-Orion which will be detailed on your card.

If you experience any symptoms of CRS whilst you are in the clinical unit (from Day 1 to Day 4), the medical team at Simbec-Orion will assess your condition and provide appropriate treatment on site as required and if necessary, i.e., if your condition worsens, you may be transferred to a local hospital (Prince Charles Hospital) for further observation and treatment.

Further to the risk of CRS, the following potential risks are also possible during the study due to the action of the drug and the way the drug is administered:

* Injection site reactions – may include mild pain, irritation, redness, swelling or rash at the injection site (this will be monitored throughout the study and treatment provided if necessary i.e. paracetamol for pain management or antihistamines to reduce any rash effects). This is expected to be a frequent side effect of the test drug.
* Development of auto-immune disease/reactions – this is extremely unlikely but has been suspected in studies of other drugs of the same family as CpG ODN D35. Again, this will be monitored during the study and other drugs interacting with the immune system. If you are starting to display any signs and symptoms of these conditions, you may be withdrawn from the study and referred for appropriate treatment if this is deemed necessary by the study doctors.

In addition to the risks of CRS, 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 other 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 drug; 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

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 participants if required following a medical emergency.

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

Study Procedures:

Blood sampling: A total of approximately 340 mL of blood (just over 1/2 of a pint) will be taken from you during this study. 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. 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 will resolve with time.

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 should remain in place for the day as well as overnight. 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.

Phototoxicity

Some drugs have an effect whereby when you take the drug and then are exposed to direct sunlight, it may induce reactions in the skin, similar to a sunburn which is known as phototoxicity. As this is the first time that CpG ODN D35 has been given to humans, there have been no studies conducted to date which have evaluated this risk for CpG ODN D35. Therefore, it is recommended that following administration of the study drug, you should avoid as much as is reasonably possible, exposure to direct sunlight until completion of the post study follow up visit.

Drug Administration

As described, the study drug will be administered via an injection (or multiple injections dependent on dose strength) into the fatty tissue layer between your skin and muscle. The site of the injections is planned to be in your stomach but if required, the locations may also include the back or side of your upper arm or the front of your thigh.

You may experience some pain or redness/skin irritation at the site of the injections; this will be monitored throughout the study and if necessary, we will take photographs of any reactions to ensure that these reactions don't become infected or spread outside of the injection site.

Cytokine Release Syndrome

As referenced in Section 9, one potential side effect of this drug is cytokine release syndrome (CRS). If you experience any of the symptoms of CRS whilst you are in the clinical unit (Day 1 to Day 4), the Simbec-Orion medical team will provide appropriate treatment as deemed necessary based on your condition.

In circumstances where you are displaying symptoms (particularly a temperature of above > 38°C) which are consistent with CRS, you will be placed on a series of monitors which will constantly record your heart rate, blood pressure, heart rhythm, oral temperature, and levels of oxygen in your blood.

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In addition to monitoring your vital signs, you will be given the following treatment if necessary:

* A cannula will be placed in order to give you fluids directly into your body.
* Administration of medications such as paracetamol to manage any increased temperature or pain.
* If you are developing any skin rash, you may also be given an antihistamine to manage the reaction.
* If your temperature increases to above 38.5°C, blood samples will be collected to measure specific components of your immune system which may be increased in CRS. These samples will also measure your level of C-Reactive Protein (CRP) which is an early marker of CRS severity.
* Additional blood samples may also be taken to monitor the function of your organs such as liver function testing.

In circumstances where your symptoms are worsening or considered moderate to severe, you will be transferred from the Simbec-Orion clinical unit to the nearest intensive care unit (ICU) which in the case of this study will be Prince Charles Hospital in Merthyr Tydfil for further treatment and management.

Symptoms of severe CRS include:

* Low blood pressure
* Levels of oxygen in the blood below 90%
* Breathing rate above 24 breaths per minute
* Temperature above 39.5°C
* Experiencing hallucinations (seeing things which aren't there), confusion, severe headache or tremors
* High levels of immune markers including CRP

The ICU will provide the necessary recommended treatment to manage your condition which may include the administration of drugs such as tocilizumab (which is an immunosuppressant drug) and steroids.

If you experience any of these symptoms whilst you are outside of the clinical unit i.e., from Day 4 to Day 7 or from Day 7 to Day 14, you should contact the medical team at Simbec-Orion using the contact details provided on your contact card to seek medical advice.

If your symptoms are worsening or are severe, then please seek medical attention from your nearest available hospital.

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 500 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 2 m distance i.e., blood sampling and will note that all beds within the unit are a minimum of 2 m apart or where this is not feasible, beds are separated by Perspex screens.

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It is noted that if you have a medical 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 -1 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.

Receipt of a COVID-19 vaccination (either the first or second dose) during the study is not permitted (from 28 days prior to the dose on Day 1 until 28 days after the dose on Day 1), and therefore, if you are invited to receive your COVID-19 vaccine during this period and still wish to receive your COVID-19 vaccine, you will be withdrawn from the study and not permitted to participate any further. We will still perform the appropriate post-study follow up assessments on your withdrawal to ensure that it is safe and appropriate to discharge you from the study.

COVID-19 vaccination is currently not recommended during the study because we do not have sufficient information on the test drug to be sure that this will not impact or have any interaction with the vaccination.

You should inform the team at Simbec-Orion if you have previously received your COVID-19 vaccine prior to screening so that this may be documented accordingly and should indicate as to whether your previous dose was the first or second vaccine dose.

However, we would note that if you are offered your COVID-19 vaccination during this restricted period, there are a number of options which you may wish to consider:

* If possible, you may request that the date of receipt of your vaccine (either the first or second dose) is changed such that it falls outside of the specified restriction window i.e., either more than 28 days prior to first dose of CpG ODN D35 or more than 28 days after the dose of CpG ODN D35.
* If you are unable to change the date of your vaccine and this falls within the restriction window, then you are free to withdraw from the study in order to receive your vaccine. As noted above, we would still perform the post-study follow up assessments to ensure that it is appropriate for you to be discharged from the study.
* If you still want to participate in the study but cannot change the date of your vaccine and have not yet received the dose of CpG ODN D35 i.e., you have only completed the screening assessments, then it may be feasible for you to be enrolled into one of the other study groups so that your vaccination date falls outside of the restriction window. However, this may not always be possible and will be dependent on which group you are currently screening for and the availability of space within the other study groups. In addition, you should note that if the length of time between your screening visit and the study group you are moving to is more than 28 days, then the screening assessments will need to be performed for a second time to ensure that you are still eligible for the study.
* If none of the above options are feasible, then you may decide to not receive your COVID-19 vaccine in order to continue participation in the study. However, you should be aware of the risks associated with this. If you opt to not receive your vaccine, then this would increase your risk for potentially contracting the COVID-19 infection. As you will be aware, although the majority of individuals who contract COVID-19 experience mild to moderate symptoms and are able to recover within a few weeks, COVID-19 can be life threatening and result in death even in individuals who are otherwise healthy and have no pre-existing health conditions. It is acknowledged that the administration of the COVID-19 vaccine is the most effective method in order to protect yourself and others from the risks of contracting the infection and therefore, you should consider carefully if you wish to turn down receipt of your vaccine in order to continue participation in the study.

In any circumstances, you may discuss all the available options with the team at Simbec-Orion in order to determine which

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option may be best for you and should ensure that you take sufficient time in order to make your decision. As always, you are free to change your mind at any point during the study and should inform the Simbec-Orion team at any stage that you are invited to receive the vaccine (regardless of whether this is the first or second dose).

Harm to the unborn child:

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 CpG ODN D35.

If your partner might become pregnant you must use a highly effective form of contraception and a condom during the trial from the first dose and for at least 3 months following the last dose of CpG ODN D35, e.g.,

* Partner using oral contraceptive + condom*
* Partner using injectable contraceptive + condom
* Partner using implant/patch contraception + condom
* Partner using Intra-uterine device (IUD)+ condom
* Partner using Intra-uterine system (IUS) + condom
* Partner permanently sterilised + condom
* Vasectomised male
* True abstinence - in line with usual lifestyle

*Note that for use of the oral contraceptive, 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.

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 for 2 years thereafter for the baby (if it is determined that the baby has been exposed to the study drug and that you were not given the placebo in the study).

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 CpG ODN D35.

In addition, you must not donate sperm until at least 3 months following the last dose of CpG ODN D35.

If your partner is already pregnant or currently breastfeeding, you must still use a condom until at least 3 months following the last dose of CpG ODN D35.

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 cutaneous 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 CpG ODN D35 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. 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 CpG ODN D35, other drugs to treat leishmaniasis or better understand the mechanisms of immune activation after exposure to CpG ODN D35. 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.

All other data collected will be stored for at least 25 years after the end of the trial by Simbec-Orion Clinical Pharmacology. Copies of these data will also be provided to the Sponsor (Drugs for Neglected Diseases initiative - DNDi). Details of who may have access to this data and what might happen to this data during this time are provided in Part 2. 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. Section 19 provides full details of what will happen to your samples.

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. 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. 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. You may ask that all previously retained samples be destroyed.

Participant Initials _____ Physician Initials _____

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 or its insurance 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 www.abpi.org (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 CpG ODN D35 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.

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 CpG ODN in disease therapy, and/or the development of tests or tools that help with detection or understanding of Leishmaniasis. This information is gathered and processed to ensure your safety and on-site monitoring of the research conduct. 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 (coded) 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 coded data, the code is strictly separated from your records. Any transfer of data outside the study site, in particular to the Sponsor, its delegates, its contractual partners, and/or collaborating researchers, takes place only in coded form. Your encrypted data may be transmitted to countries which do not have the same level of data protection as within 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 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 coded data will be used.

Your rights to access, change, erase 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 a coded 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, correct and request the erasure of your data, however these rights might be limited due to other requirements and will be decided on a case by case basis. 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

Participant Initials _____ Physician Initials _____

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. In addition, if it is determined that your blood sample which is taken for autoantibody analysis needs to be analysed (because you have developed signs and symptoms of autoimmune reactions/disease following administration of CpG ODN D35), then your GP will also be informed of this and if deemed necessary, you may be referred for further follow up with your GP.

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

Your samples and data are stored at the Simbec-Orion Clinical Pharmacology site in Merthyr Tydfil and 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 and COVID-19 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 samples which are taken to determine the concentration of CpG ODN D35 in the blood, the measurement of cytokines and chemokines, and to measure PBMCs (a type of blood cell) will be processed onsite at Simbec-Orion Clinical Pharmacology and sent for analysis at a laboratory called Oncodesign Biotechnology based in France, and to the University of Tokyo in Japan.

In addition to this laboratory, and as deemed necessary by the study sponsor, the samples may also be sent for further analysis to any laboratory chosen by the study sponsor who may be based anywhere worldwide.

These samples will be analysed and stored for a period of up to 10 years 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.

As referenced previously, we will also take a blood sample from you in order to perform measurement of mRNA markers and how these change following exposure to the study drug. Further details of this analysis are described in section 20. This analysis will be conducted at a suitably qualified laboratory chosen by the study sponsor based anywhere worldwide and samples stored for a period of up to 10 years before they are destroyed.

All of the analysis described above is considered mandatory and if you do not wish to consent to this analysis, then you will not be able to participate in the study.

The blood sample which is taken on Day 1 prior to dosing for the purposes of measuring levels of autoantibodies will be processed on site at Simbec-Orion. The samples will initially be stored on site at Simbec-Orion; however as necessary during the storage period, the samples may be moved to an external storage facility for longer term storage. This may be based anywhere worldwide. As described in Section 5, this sample will only be analysed if you develop any signs or symptoms which would be indicative of autoimmune reactions/disease. If it is determined that this sample needs to be analysed to determine if you had pre-existing levels of autoantibodies, the sample will be sent for analysis to a laboratory chosen by the study sponsor who may be based anywhere worldwide. The results of this analysis will then be reported to the sponsor and Simbec-Orion team who will

then inform you as a participant and your GP as necessary. If required, the team will also advise you of any follow up assessments or treatment which may be required to manage this condition if it is determined that your condition has developed as a result of the study drug. If this is not the case, then you will be advised to follow up with your GP accordingly to determine the cause of your condition.

In any circumstance, these sample will be stored and held by the study sponsor for a maximum period of 3 years, after which they will be destroyed.

All of the data mentioned above will be stored in a form which is not personally identifiable i.e., using only the subject number assigned to you during this study.

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 CpG ODN D35 using the samples collected during this study, development of other drugs to treat leishmaniasis, or better understand the mechanisms of immune activation after exposure to CpG ODN D35. 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 10-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 specific genetic testing planned in this study. However, blood samples will be taken at set time points during the study which will be used for the measurements of specific messenger RNA (mRNA) markers.

mRNA is responsible for carrying the genetic information copied from your DNA which instructs the production of proteins. The process of copying your DNA into mRNA is called transcription.

Transcription is a process which can be affected by different drugs i.e., some drugs can cause more transcription and therefore more protein generation and other drugs can inhibit or slow this process.

In the context of this study, the blood samples will be used to determine if the study drug has any effect on your mRNA markers which are associated with the production of cytokines and chemokines, which regulate your immune response. Changes in these markers could demonstrate that the drug is having the desired effect in the body through the stimulation of cytokine production.

mRNA is generated as a copy of your DNA, but it is not possible for you to be identified as an individual from this analysis.

Results from this analysis will not be shared with Simbec-Orion or with you as a research participant. The rationale for this is that the results are purely for research use only and only for the purposes of exploring and identifying the effect of CpG ODN D35 on your mRNA markers. 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.

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 Annelize Koch, 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 Annelize Koch

Project Manager: 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 IMP. 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.

Participant Initials _____ Physician Initials _____

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**

Participant Initials _____ Physician Initials _____

CONSENT FORM

Simplified Title: A study to investigate the safety, tolerability and activity of CpG ODN D35 in healthy volunteers.

Study Number: RD 777.35000 (DNDi-CpG-01)

IRAS ID: 297265

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), Chemin Camille Vidart, 15, 1202 Geneva, Switzerland

Simbec-Orion Clinical Pharmacology ID Number					

Screening Number:			
Subject Initials			
Date of Birth (DD/MMM/YY):	____ ____ / ____ ____ ____ / ____ ____		

NAME OF CHIEF INVESTIGATOR: Dr Annelize Koch

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 12 May 2021 (Version: v2.0) 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 12 May 2021 (Version: v2.0) 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.	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.	
10.	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.	
11.	I give consent for any photographs to be taken of any injection site reactions as required.	
12.	I understand the risks and implications of cytokine release syndrome (CRS) and am willing to receive any treatment and management as necessary to manage my condition appropriately.	
13.	**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.	

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 13 in table above)			
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)

Participant Initials _____ Physician Initials _____

INFORMATION SHEET FOR HIV ANTIBODY, HEPATITIS B & C TESTING

Simplified Title: A study to investigate the safety, tolerability and activity of CpG ODN D35 in healthy volunteers.

Study Number: RD 777.35000 (DNDi-CpG-01)

IRAS ID: 297265

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), Chemin Camille Vidart, 15, 1202 Geneva, Switzerland

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 protocol, 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 your GP or a 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.

Participant Initials _____ Physician Initials _____

INFORMATION SHEET FOR COVID-19 PCR TESTING

Simplified Title: A study to investigate the safety, tolerability and activity of CpG ODN D35 in healthy volunteers.

Study Number: RD 777.35000 (DNDi-CpG-01)

IRAS ID: 297265

Name of Sponsor: Drugs for Neglected Diseases initiative (DNDi), Chemin Camille Vidart, 15, 1202 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 -1 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 2-5% 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.