RPL ID Number: <INSERT VDB LABEL>
Screening Number:

Participant Information Sheet/Informed Consent Form

Clinical Trial Title

A Phase I, Single Centre, Randomised, Interventional, Open-Label, Cross-Over Study to Evaluate the Pharmacokinetics (PK) and the Safety and Tolerability of a Total Daily Dose of 900mg of TETA 4HCL, Comparing a New Once Daily TETA 4HCL Formulation (300mg) (3x300mg Trientine Base Tablets, OD) with the Current Marketed Cuprior® Formulation (150mg) (3x150mg Trientine Base Tablets, BD) in Adult Healthy Male and Female Participants

Protocol Number: ORPH-131-012

IRAS ID: 1009060

Orphalan SA

226 Boulevard Voltaire, 75011, Paris, France

Dear Participant,

We would like to invite you to take part in our clinical trial involving healthy participants. Joining the trial is entirely up to you, but before you decide, we would like you to understand why the clinical trial is done, what the clinical trial involves, and how we will use the information we collect about you.

Please take time to read the following information carefully and discuss it with others if you like. Please ask us if there is anything that is not clear or if you would like more information.

Once you have read this Participant Information Sheet, the Research Doctor will go through this information with you, to help you decide whether or not you would like to take part and answer any questions you may have.

Key trial Information	
Who is funding and conducting this trial?	Orphalan SA (a pharmaceutical company based in France), also referred to as the Sponsor.
Lead Research Doctor(s):	Dr Thomas Ashdown & Dr Ulrike Lorch
Trial Unit:	Richmond Pharmacology, Ltd. 1A Newcomen Street, London Bridge London, SE1 1YR, UK
What does the investigational medicine do?	Trientine tetrahydrochloride (TETA 4HCl) is a drug that is designed to treat Wilson's disease and is approved in the UK. Wilson's disease is caused by an excess of copper in the body. Although the body needs some copper to function properly, an excess of it can cause a build-up leading to damage of the liver and nervous system. TETA 4HCl attaches to copper in the body. This allows for the copper to be removed in the urine to lower the copper levels in the body.
Why is the clinical trial being conducted?	A TETA 4HCl tablet has already been approved for use in Wilson's disease patients and is currently marketed in the UK under the name Cuprior®. Patients normally have to take their tablets 2-4 times a day. The Sponsor has created a new tablet, which contains more TETA 4HCl, which they believe patients will only have to take once a day. This trial will compare the new TETA 4HCl tablet to the currently approved Cuprior® tablet. The trial will look at the levels of the drug in the blood after taking the different tablets (either once in the morning for the new tablet compared with morning and early afternoon for the currently approved tablet) and compare how safe and well tolerated the two different tablets are.
How many participants are planned in this trial?	Up to 26 healthy adult participants will take part in the trial. All participants will receive both the new TETA 4HCl tablet(s) and the approved Cuprior® tablet(s) at different visits at least 5 days apart.
Who is allowed to take part in this trial?	The Research Doctor will determine if you qualify to participate, but key requirements include that you: • Are aged between 18 to 40 years old • Meet all inclusion criteria • Do not meet any of the exclusion criteria (conditions that are not allowed) More information about the inclusion/exclusion criteria and trial rules is given in sections 2 and 3.
What is the expected duration of the trial?	This clinical trial will take approximately 7 weeks including the screening period.

What will I have to do?	You will be required to attend the trial unit for a screening visit, complete 2 separate in-house stays (consisting of 4 days and 3 nights each) and attend a follow-up visit. You will be admitted to the unit on Day -1 for both in-house stays. On the dosing day (Day 1) of both stays, you'll receive a dose of either the new TETA 4HCl tablet or Cuprior® (please refer to **Figure 1**)**.** The number of tablets taken and how many times in the day will vary based on the type of tablet you are receiving. Half of the participants will take the new TETA 4HCl tablets first, and then Cuprior®, after a certain period (known as the washout period which will be 5-10 days), ensuring the old drug is out of their system. The remaining participants will take the same tablets in the opposite order, as shown in **Figure 1**. For the duration of the clinical trial, you will undergo tests and procedures before and after the drug is administered as outlined in the **Trial Calendar**. Additionally, you will be asked to follow the trial rules and restrictions. This is for your safety. Some medicines, tobacco, alcohol, or supplements, might affect the way the trial drug is processed by your body.
Are there risks to participating?	There are potential risks (called side effects) such as allergic reactions, and soreness or pain from the blood draws. A Research Doctor will discuss the potential risks in detail with you.
Is there a benefit to participating?	The trial drug you will receive is being given to you for research purposes. You will not receive direct medical benefit. It is hoped that the information collected in this trial will help patients with Wilson's disease in the future.
Can I stop participating?	You are free to stop participating in this trial at any time. Please notify a member of the research staff. You do not need to give a reason and it will not impact your future medical care.

1. Summary of the clinical trial

What is the purpose?

The investigational drug used in this clinical trial is Trientine tetrahydrochloride (TETA 4HCl) which is a drug that is designed to treat Wilson's disease.

Wilson's disease is an inherited disease (an illness that is passed on from both parents) where patients end up with too much copper in their bodies. This is a rare disease that affects less than 2000 patients in the UK. Normally, the body needs some copper to function but with this disease, the copper isn't processed properly. As a result, patients are unable to remove the copper, resulting in a gradual build-up in the body. This can then lead to liver damage and problems with the nervous system. TETA 4HCl attaches to the excess copper in the body and then it is removed in the urine.

A TETA 4HCl tablet has already been approved by the drug regulatory agencies for use in Wilson's disease patients and is currently marketed under the name Cuprior®. Patients normally have to take this 2-4 times a day. The Sponsor have created a new tablet, which contains more TETA 4HCl, which they believe patients will only have to take once a day. The new TETA 4HCl tablet is not yet approved for use by the drug regulatory agencies. Therefore, it can only be used in research studies such as this one.

What are the main aims?

To assess the levels of TETA 4HCl and its breakdown products (metabolites) in the blood and how long they remain there (pharmacokinetics) and compare this with the currently approved marketed tablet (Cuprior®).
To assess and compare the safety and tolerability of the new TETA 4HCl tablet with the approved Cuprior®.

What are the key elements?

In this trial, all participants will receive both treatments (new TETA 4HCl tablet and Cuprior® tablet). All eligible participants will be randomised (allocated to a treatment sequence by chance, like flipping a coin) as shown in **Figure 1**. Half of the participants will take the new TETA 4HCl tablets first and then after the washout period of 5-10 days, they will then take Cuprior® (this is treatment sequence 1). The remaining participants will receive treatment sequence 2, as shown below. The new TETA 4HCl tablet will be given as 3 tablets, once in the morning, with 240ml of water after overnight fasting. Cuprior® will be given as 3 tablets twice in the day, once in the morning after overnight fasting and 8 hours later in the afternoon, after a minimum of 2 hours of fasting. As this is an open-label trial, you and the research doctors will know what drug you are taking during each period.

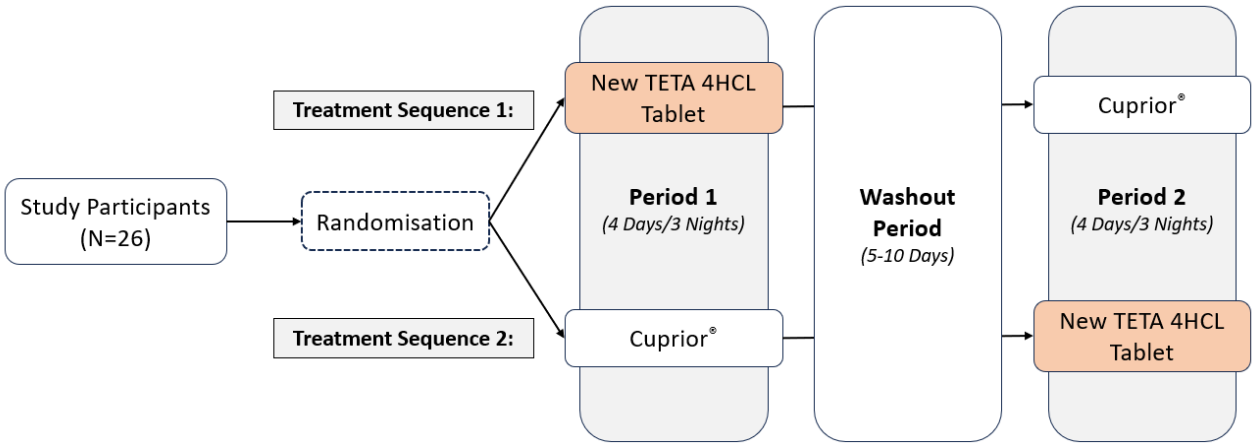


Figure 1. Randomisation Process

What are the possible benefits?

The new TETA 4HCl tablet and Cuprior® medication that you will receive in this trial, are being given to you purely for research purposes. It is not intended that you will receive any benefit from them. Ultimately, it is current and future patients suffering from Wilson's disease that may benefit from this research. New, more effective, and convenient medicines can only be developed by performing research and we would like to thank you for considering participating in this clinical trial.

What is the trial journey?

Screening Visit

- You will be required to attend a screening visit scheduled within 28 days before the first dosing day to ensure that you meet all of the trial eligibility criteria.
- Screening will be conducted over one day or may be divided into more than one day if necessary.

Treatment Period

- Participation requires two in-house stays of 4 days and 3 nights. The in-house stay may be extended, if necessary, for your clinical safety.
- You will be admitted to the unit on Day -1 of the **first** in-house stay (the day before the dosing).
- You will receive either the new TETA 4HCl tablets (3 tablets, once only) or Cuprior® (6 tablets in two sittings over 24 hours) on Day 1 with 240ml of water.
- After dosing, you will be closely monitored by medically qualified staff and undergo standard safety assessments and blood samples to measure levels of the trial medicine in the body*.
- You will be discharged from the unit on Day 3.
- You will then return to the unit after the washout period (5-10 days between drug administration days) for the **second** in-house stay. This time you will receive the other drug.

Follow-Up Visits

- You will be required to attend the unit for a follow-up visit on Day 7 **of the second treatment period**.

In total, you must be prepared to attend the trial unit on 4 occasions (unless the doctor requests further visits for safety reasons). You will only need to attend one follow-up visit unless the research doctor says otherwise.

*The standard assessments that will be conducted during the clinical trial include safety blood and urine laboratory tests, vital signs, physical examinations, ECG (electrocardiogram – electrical heart recording), pharmacokinetics (measurement of medicine levels in the blood) and observations of any adverse events (side effects).

Do I have to take part?

Your participation in this clinical trial is voluntary, and you may withdraw your consent to take part at any time, without stating your reasons.

Will my GP be involved?

Yes, by signing a separate General Practitioner (GP)/Medical Practitioner Consent Form, you will give Richmond Pharmacology Ltd permission to contact your GP. This is so that your GP can tell Richmond Pharmacology Ltd if there is any reason why you should not take part in this Orphalan SA sponsored clinical trial or any future Richmond Pharmacology sponsored or conducted clinical trials. By signing the form, you are also giving Richmond Pharmacology permission to inform your GP of any abnormal results seen at screening or during the clinical trial. This is because your GP needs to be aware of any change in your health status. If a clinically significant abnormal result is identified, a study doctor will make every reasonable effort to contact you to thoroughly explain the findings and the potential implications. During this discussion, if you do not want your GP to be informed you must tell us. We will respect your wishes unless sharing the information is justified in the public interest. With respect to any other Richmond Pharmacology sponsored or conducted clinical trials that you may participate in, unless it is an Orphalan SA sponsored clinical trial, Orphalan SA shall have no responsibility or liability to you or Richmond Pharmacology regarding contacting, obtaining medical records and information from your GP, or otherwise communicating with your GP as outlined in the separate General Practitioner (GP)/Medical Practitioner Consent Form.

2. Am I eligible for this clinical trial?

You may be eligible to take part in this clinical trial if you:

	Are a male or female aged between 18 to 40 years.
	Weigh 50 kg or more and have a body mass index (BMI) of 18 to 25 kg/m^2.

	Are generally in good health based on screening examination, including medical history, physical examination, blood pressure, pulse rate, temperature, respiratory rate, ECG assessment, urine, and blood results.

You <u>will not be eligible</u> to take part in this clinical trial if you:

	Have a medical history of any other illness, condition, or disease that in combination with the trial drug would pose a risk to your safety.
	Have any acute illness (e.g. vomiting, fever, diarrhoea) within 7 days of the first dosing day.
	Have had any major surgery or illness within 12 weeks before Day 1 dosing.
	Have any relevant drug allergies or a condition that may make you react badly to the drug that will be administered in this trial.
	Use prescription (excluding hormonal contraceptives or hormone replacement therapy) within 30 days of dosing or over-the-counter medications (including herbal remedies and supplements) within 14 days of dosing on Day 1.
	Have received another investigational medicine within 90 days before dosing on Day 1 or exposure to more than 3 investigational medicines within 12 months of Day 1 dosing.
	Test positive for drugs of abuse/alcohol at screening or on day -1 of each period.
	Have a history of use of tobacco products within 6 months of screening or test positive for it at screening.
	Have donated or lost more than 450ml or more of blood or plasma within 16 weeks before the trial and or intend on donating blood within 16 weeks of the trial ending.
	Are pregnant or breastfeeding.
	Have a history of drug or alcohol abuse.

3. What am I expected to do during the trial?

You must be willing to adhere to the rules and restrictions stated below and attend each of the scheduled visits as detailed in the **Trial Calendar**.

It is also important that you tell our clinical staff about any other medication you are taking before and during the clinical trial. In addition, you must tell the Research Doctor immediately if you or your partner become pregnant during the trial.

If you have a medical need to take any medications and your GP/another Doctor prescribes or advises you to take them, you should follow the medical advice. However, please inform the Research Doctor as soon as possible using the contact details on the Participant ID card that you will be given or the contact information in Section 10 of this document.

Trial Rules

Here is a list of things you must do during the clinical trial:

Contraception	**If you are a female participant of childbearing potential[a]:** You must use a highly effective method of contraception during the trial period and for at least one complete menstrual cycle before dosing and for at least 1 month after the last dosing day of the trial. Highly effective methods of contraception include: • Combined (oestrogen- and progestogen-containing) contraceptives (e.g., oral pill, vaginal rings, and patches) • Progestogen-only contraceptives (e.g., oral pills, injections, and implants) • Intrauterine hormone-releasing systems (placed in the uterus and slowly release a low dose of hormones) • Intrauterine device (hormonal or copper) • Bilateral tubal occlusion (surgical blocking of the fallopian tubes) • Infertile male partner (e.g. vasectomised, bilateral orchidectomy or any other reason with documented evidence) • Sexual abstinence[b] [a] Women of childbearing potential are defined as women who are fertile following menarche (the first occurrence of menstruation) until becoming postmenopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy (surgical removal of the fallopian tubes), and bilateral oophorectomy (surgical removal of the ovaries).	

	[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. If abstinence is your preferred and usual lifestyle before starting the trial, you will be asked to refrain from intercourse from one complete menstrual cycle before the first dosing until 1 month after the last dose in the trial and be exempt from contraception. **If you are a female of non-childbearing potential:** You do not require contraception. Confirmation of post-menopausal state will be undertaken by blood testing at the unit.	
	If you are a male participant: You must agree to the following during the trial duration and for at least 1 month after the last dose of the trial medicine: a. Be abstinent from heterosexual intercourse with female partners of childbearing potential. OR b. Use a male condom (during intercourse with a female partner of childbearing potential to prevent the transfer of trial medicine to the female partner or foetus/baby, and they should also be advised to use a highly effective method of contraception), this is still required even if you are infertile (e.g. vasectomised, permanently sterile following bilateral orchidectomy (removal of both testicles), or any other documented cause of infertility).	
Meals	You will receive standardised meals, served at scheduled times throughout your in-patient stay. You are required to consume all your meals. These meals may contain meat and provision for diets that are either meat-free or free from certain meats is not available as part of this clinical trial.	

	You will be required to fast overnight before dosing. Once you have been dosed on Day 1, you will be required to fast for one hour (no water for this hour too). For the dosing of Cuprior®, participants will need to have fasted for 2 hours before the second dose and for 1 hour after.	
Unit rules	You will be required to observe and adhere to the unit rules during your in-house stay as stated in the Volunteer Charter and Unit Rules (unit regulations).	

Trial Restrictions

Here is the list of things you must not consume or do during the clinical trial:

Smoking (tobacco and/or nicotine-containing products)	You must not use tobacco and/or nicotine-containing products within 6 months before the dosing day and until trial completion/last visit. Richmond Pharmacology is a non-smoking site and smoking is not allowed anywhere on the grounds.	
Alcohol	You must not consume alcohol within 48 hours before the dosing on Day 1 (of both dosing periods) and 48 hours before the follow-up visit.	
Strenuous physical activity	You may not participate in strenuous physical activity 48 hours before screening, admission, and follow-up visit. Strenuous physical activity means more than your normal regime, but you can discuss this further with the Research Doctor if you are unsure about what this means. You should not start new physical training activities during the trial until completion.	
Prescription or over-the-counter medication	You must not use any prescriptions (excluding hormonal contraception or hormone replacement therapy) within 30 days before the dosing day and throughout the trial. Over-the-counter medications (including remedies and supplements) must not be used for 14 days before the dosing day 1 and until trial completion (last visit). Exceptions: Paracetamol ≤ 2 g per day (but the research doctor should still be notified).	

Caffeine- or Xanthine-containing products	You must not consume caffeine or xanthine-containing products (for example: coffee, tea, cola drinks and energy drinks) for 48 hours before the dosing day and each follow-up visit.	
Blood and plasma donation	You are not allowed to donate blood or plasma within 16 weeks before the dosing day until 16 weeks after the trial completion (last visit).	
Energy drinks	You must not consume any energy drinks containing taurine or glucuronolactone (e.g., Red Bull) within 48 hours before the dosing day and each follow-up visit.	
Recreational drugs	Under no circumstances are you allowed to take drugs of abuse for the duration of the clinical trial. This could lead to unpredictable risks, which can seriously damage your health.	

Please note that this is not an exhaustive list of the eligibility criteria. The Research Doctor will discuss this with you in detail.

4. What happens at dosing?

All participants will receive both the new TETA 4HCl tablets and the approved Cuprior®. Both planned doses provide a total daily dose of 900mg of TETA 4HCl :

New TETA 4HCl tablet
3 tablets of 300mg given once in the morning

Cuprior®
6 tablets of 150mg divided into two doses (3 tablets in the morning and three tablets in the afternoon)

5. What type of tests and procedures will be done?

Below is the summary of the tests and procedures you will have performed during the trial after you have provided written informed consent. Please refer to the **Trial Calendar** for more information on which tests and procedures are performed during each of your trial visits.

COVID-19 & Influenza test	You will be required to have a throat and/or nasal swab for COVID-19 and influenza screening before you enter the unit, and once daily during your inhouse stays. In addition, a check of your health records to confirm you are fully vaccinated against COVID-19.	
General health, symptoms, and medical history	You will be asked questions to gather a full medical history including questions about past or present medical problems or surgeries, allergies to medications, your activity level, smoking status, alcohol, and tobacco consumption as well as information on age, gender, and race. Throughout the trial, the staff will regularly ask questions about your health. We will also record any adverse events (side effects) you may have during the trial.	
Physical examination	A Research Doctor will perform a physical examination (medical check) to assess your body systems.	
Height, weight, and BMI	The trial staff will measure your height, weight, and BMI.	
Electrocardiograph (ECG)	This trial staff will regularly check how well the heart is functioning. This will be done by placing small sticky pads on your chest, shoulder, and hips. The pads are connected by wires to a machine that will measure the electrical activity of your heart. Before each ECG you need to lie down for at least 10 minutes.	

Vital signs	The trial staff will regularly check your vital signs including blood pressure, pulse, body temperature, and breathing rate.	
Urine samples	Urine samples will be collected to: • Test for drugs of abuse • Check your general health. • Check if you are of childbearing potential and to check if you are pregnant (females only). • Check nicotine levels	
Blood samples	Blood samples will be collected to: • Check if you are of childbearing potential and to check if you are pregnant (females only). • Check your general health (safety blood samples) • Measure the pharmacokinetic properties of the trial drug.	
Alcohol breath test	A breath test will be performed to test for alcohol.	
Trial drug administration	At each dosing timepoint, you will be given three tablets which you must swallow with 240ml of water. You will be asked to take the medication at an exact time and have a mouth inspection to ensure you have taken the medication.	

Additional blood test

You must also agree to an additional blood test being performed before the start of the clinical trial to test for HIV 1 and 2, Hepatitis B, and Hepatitis C. If you are found to have a positive result, the Research Doctor will contact you and explain the results to you, and we will inform your GP (if applicable). We may request a repeat blood test to be done to confirm the diagnosis. Please note that you will not be able to participate in this clinical trial if you test positive for HIV, Hepatitis B, or Hepatitis C or refuse to allow the collection of blood for these tests.

Blood volume

The total volume of blood that will be taken over the duration of the clinical trial will be less than 350mL, approximately 70 teaspoons. This includes any additional blood samples that may be undertaken for safety reasons and to ensure the quality of the clinical trial data.

COVID-19 procedures and precautions

Please note that you will be required to have a throat/nasal swab for COVID-19 and influenza at regular intervals i.e., before entry to the Richmond Pharmacology Unit and ad-hoc (as required) during your in-house stay. Please also note Public Health England will be notified within 72 hours if you test positive for SARS-CoV-2, in line with our legal duty. By signing this consent, you are allowing us to also use your anonymised COVID-19 test results for research purposes.

Wearing of face masks at the unit:

Coronavirus (Covid-19) usually spreads by droplets from coughs, sneezes, and speaking. These droplets can also be picked up from surfaces if you touch a surface and then your face without washing your hands first. This is why social distancing, regular hand hygiene, and covering coughs and sneezes are so important in controlling the spread of the virus.

The best available scientific evidence is that, when used correctly, wearing a face covering may reduce the spread of coronavirus droplets in certain circumstances, helping to protect others.

During your time with us at Richmond Pharmacology, you will be required to wear a face mask at all times whilst in the unit. This may change based on our current COVID-19 policy.

Possible changes:

The COVID-19 pandemic is an ongoing global healthcare crisis and Richmond Pharmacology is constantly adapting our health and safety measures in line with the latest scientific evidence and Government guidance. You will be fully informed of any changes to our health and safety policy, including the requirement to wear face masks and other personal protective equipment as soon as practically possible.

6. What are the possible risks and discomforts of taking part in the trial?

The trial drug may cause some side effects. You may experience none, some, or all of those described below. Should you develop any new symptoms of an illness or become unwell during the trial, you will be examined by a Research Doctor, which may involve additional safety tests (including urine and blood tests, vital signs, and ECGs). The Research Doctor will perform a clinical assessment and ensure your condition is managed appropriately. This may involve taking additional medication or having a procedure. The risks and benefits of any additional treatment will be explained to you. You may be referred to a hospital or another clinical care setting for further management if, in the

opinion of the Research Doctor, your condition cannot be safely managed within the Richmond Pharmacology unit. This includes referrals for private specialists or general practitioner assessments.

The new TETA 4HCl tablet, is similar to the reference medicine, Cuprior® (contains TETA 4HCl as the active drug), which has been used to treat Wilson's disease since 2017. Cuprior® has some possible side effects, including:

Common (1 in a 100 to 1 in 10 people)

- Nausea (sickness)

Uncommon (1 in 1000 to 1 in 100 people)

- Sideroblastic anaemia (low red blood cell levels when the body has enough iron but it is not being used)
- Skin rash
- Pruritus (itchy skin)
- Erythema (redness of the skin)

Not known (cannot be estimated from the current data)

- Iron deficiency anaemia (low red blood cell levels due to not enough iron)
- Duodenitis (inflammation of the small intestine)
- Colitis (inflammation of the bowel)
- Urticaria (hives)

The trial team is taking steps to manage these risks, including:

- Excluding participants with any underlying medical conditions that could make them more at risk of suffering from side effects.
- Monitoring participants closely.
- Taking safety blood tests and performing physical examinations at regular intervals.

We believe the side effects of the new TETA 4HCl tablet will be very similar to Cuprior® as they both contain the same active drug (TETA 4HCl). Although unlikely, because the new TETA 4HCl tablet has not been tested in humans before, there may be side effects that we cannot predict. However, for the duration of the trial, all side effects will be collected, and the data will be analysed to compare the safety profile of the established TETA 4HCl tablets with the new TETA 4HCl tablets.

Richmond Pharmacology Ltd is a specialist clinical trials unit that regularly conducts trials where drugs are given to people for the first time. There are trained doctors and clinical staff on-site and procedures in place (approved by the authorities) to deal with side effects that arise.

Risks associated with pregnancy and breastfeeding

If you are a woman of childbearing potential:

- You must not plan to become pregnant during the trial as nothing is known about the effect of the trial drug on pregnancy, breastfeeding, or an unborn foetus.
- You must use a highly effective method of contraception during the trial and for 1 month after the last dose of the trial drug. Please refer to 'Acceptable methods of contraception' (Section 3: What am I expected to do during the trial?) for more information.

The Research Doctor will discuss contraception with you, and you will be asked to have pregnancy tests during the trial. If you think you may have become pregnant during the trial you must tell the Research Doctor immediately. If you are pregnant or breastfeeding, you will not be able to participate in the trial. If you become pregnant during the trial, you must tell your Research Doctor immediately so we can help decide on appropriate action. We would discuss referral for specialist counselling on the possible risks to your unborn baby and arrangements will be made to monitor the health of both you and your unborn baby. The Research Doctor will collect information about your pregnancy and the health of you and your baby.

If you are a man whose partner is of childbearing potential:

- You must use barrier contraception from screening and for at least 1 month after the last dose of the trial drug. This is still required even if you are infertile (e.g. vasectomised, permanently sterile following bilateral orchidectomy (removal of both testicles), or any other documented cause of infertility). Female partners of male participants are advised to use highly effective contraception (detailed in Section 3: What am I expected to do during the trial?) during the trial and for 1 month after the last dose. This is to stop the transfer of the trial drug to your partner, foetus, or baby, as we do not know if TETA 4HCl is safe for an unborn baby.

If you think your partner may have become pregnant during the trial tell the Research Doctor immediately. If your partner becomes pregnant, she will be asked to sign and date a separate informed consent form for her permission to collect information about the pregnancy and its outcome.

Risks associated with trial procedures:

Blood pressure	Blood pressure 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.	
Blood sampling	During the trial, blood will be drawn for testing. You may experience discomfort and/or soreness when the needle is inserted and removed, and a small bruise may appear. Very rarely, a vein can become blocked, or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it typically will resolve with time. There may be other side effects such as fainting, redness, bleeding, or infection.	

	The clinical staff may decide to use a cannula (a small plastic tube) placed in your arm using a small needle because it allows several blood samples to be taken without having to insert a needle each time. This cannula may remain in place for 24 hours following your dose of the trial medicine, after which it will be removed. As with all uses of a cannula, there is a small chance of infection, but every medical precaution will be taken to prevent this from happening.	
ECG	Minor skin irritation could develop from the adhesive used on the pads. 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 plasters, these sticky pads may be uncomfortable to remove and in rare cases may cause some skin irritation.	

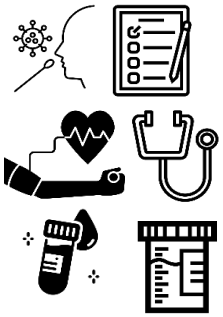
7. Trial Calendar

Day -28 to -2 (Screening)
1 or more visits
In-person Clinic Visit(s)


If you have already carried out screening assessments for another trial at Richmond Pharmacology, this informed consent form will allow us to use those results in this trial to avoid repeat procedures.

Day -1	**Day 1**	**Day 2**	**Day 3**
In-house Treatment Periods			
Overnight stay			

Day 7 (Follow up)
In-person Clinic Visit(s)

There will be a washout period of 5-10 days (between treatment doses) before the 2nd in-house period. The in-house Treatment Period calendar will be the same for when you return for the second in-house visit.

8. How will I be reimbursed?

In recognition of the time and effort involved in taking part in this clinical trial, you will be paid £833.33 on completion of the clinical trial, once follow-up results are confirmed, checked by the Research Doctor, and confirmed there are no safety issues. i.e., the Research Doctor considers your participation in the clinical trial to be completed.

We want you to cooperate with us to achieve the objectives of the clinical trial, so if you are dosed, We will give you a compliance payment of £416.67 for your satisfactory compliance with this document (Participant Information/Informed Consent Form), the Richmond Pharmacology Volunteer Charter and all unit rules (unit regulations). However, the compliance payment is issued at the discretion of Richmond Pharmacology, meaning Richmond Pharmacology may not pay these monies if there is a justified reason not to do so within the terms of the contract with you the participant.

The total amount that you could be paid for the clinical trial is £1,250.00. Payment will be made to you up to 21 working days after completion of the clinical trial. You will be paid for the time you give up for the clinical trial site and this payment is only for time and NOT linked to risk or inconvenience. Therefore, payment is proportional to the time you spend on the clinical trial i.e., payment may be

reduced or increased depending on your duration in the clinical trial (if you are required to attend the unit for fewer or more days than stated in the Clinical Trial Plan). You should not view participation in this clinical trial as equivalent to employment and under no circumstances should you participate in more than one clinical trial at a time.

Please note that the clinical trial payment includes travel expenses.

If you are dosed with the trial drug and are required to attend the unit for a repeat test (outside of scheduled or requested visits prolonging your participation in the clinical trial) you will be paid £80 for a day visit or £100 for an overnight visit plus a contribution towards your travel expense of £20. This is applicable for each visit (i.e., in addition to the visits above) that you are required to attend.

If you are withdrawn from the clinical trial for any reason, either voluntarily or non-voluntarily, you will be reimbursed for your time according to Table 1 below.

REASON for WITHDRAWAL	RE-IMBURSEMENT	COMPLIANCE PAYMENT
Unwell/Illness related to the clinical trial or medicines*	Pro-rata**	Full
Unwell/Illness unrelated to clinical trial or medicine *	Pro-rata**	Full
Entire clinical trial stopped	Pro-rata**	Full
Non-compliance or voluntary withdrawal	None	None

Table 1: Withdrawal reimbursement plan

*As judged by the Research Doctor.
**Calculated according to the actual time spent in the clinical trial in relation to the total clinical trial period.

For admission and to make sure that we start the clinical trial with the right number of participants, we will book more participants than will be dosed. The decision as to who is included on Day 1 of the clinical trial will be decided by the Research Doctor who will take into account your past medical history and the availability and quality of your medical history. The amount you will be paid if you are admitted yet not dosed is £150.

Should you not wish to receive payment for this clinical trial, then we suggest that you nominate a charity of your choice, and we will arrange for a donation of the amounts that would otherwise be due to you.

It is your responsibility to manage your own tax affairs. Information on how the clinical trial payments may impact your tax responsibilities can be found on the following website: www.hmrc.gov.uk/manuals/eimanual/eim71105.htm. For any further information, please contact your local tax office.

9. What could change during the trial?

Trial termination

If the clinical trial stops or if you decide to withdraw from the clinical trial early, you understand that we will keep the information about you that we have already obtained and that we can process this information in accordance with the clinical trial protocol and this Informed Consent Form.

Please refer to Appendix 2 for more information.

The Research Doctor may also decide to remove you from the clinical trial due to illness, side effects, new information on the trial drug or if you are not following the clinical trial rules and restrictions. In addition, the Sponsor may end your participation in the clinical trial at any time without your consent. You are strongly advised to attend a follow-up visit if you do not continue with the clinical trial for any reason, this is for your safety.

New information

Sometimes during a research project, new information becomes available about the treatment/investigational drug that is being studied. If this happens, the Research Doctor will tell you about it and discuss with you whether you want to continue in the clinical trial. If you decide to withdraw, the Research Doctor will make arrangements to continue your care if this proves necessary.

If you decide to continue in the clinical trial, you will be asked to sign an addendum to the version of the consent form you previously signed. On receiving new information, the Research Doctor might consider it to be in your best interests to withdraw you from the clinical trial.

Richmond Pharmacology and the Sponsor reserve the right to terminate your participation in the clinical trial, at any time without your consent.

10. What if there is a problem?

Any complaint about the way you have been treated during the clinical trial or any possible harm you may suffer will be addressed. Reimbursement will be available for any injury attributable to the administration of the investigational drug or any clinical intervention or procedure within the clinical trial. Detailed information is given in Appendix 1.

WHO SHOULD I CONTACT FOR MORE INFORMATION OR IF I HAVE QUESTIONS?

If you have a question, concern, or complaint about any part of this study, then you should contact our Volunteer recruitment team who will do their best to help or connect you to the study doctor or a member of the study team to ensure that your queries are discussed and adequately addressed.

Name: Volunteer Recruitment team

Phone: +44 (0) 207 042 5800 Monday – Friday: 08h00 – 19h00.

Additionally, the Research Doctor and his/her staff will be pleased to help if you have any further questions about this clinical trial. Should you have any urgent questions or experience a side effect, a member of staff is contactable on one of the telephone numbers below 24 hours a day.

A side effect is any illness, symptom or discomfort you develop at any time during the clinical trial. The illness/symptom might be related to the clinical trial, or it might be something completely unrelated like a cold or a headache or an injury. However, **you must let us know about all of these events, even if you think that they might not be serious or important**.

Prior to leaving the unit after you have been dosed, you will be provided with a Participant ID Card. You should always carry this card while you are involved in the clinical trial. The Participant ID Card contains your details (Richmond Pharmacology ID, forename, surname, and date of birth along with the clinical trial code C23030 and the following information (in italics).

I am currently participating in a clinical trial. I may be taking an investigational medicine. In case of an emergency, please contact Richmond Pharmacology.

Richmond Pharmacology Ltd
1A Newcomen Street
London Bridge
SE1 1YR

0207 042 5800
Monday – Friday: 08h00-19h00

079 7942 2946
24 hour Medical emergency (for any medical concerns)

www.richmondpharmacology.com
www.trials4us.co.uk

The medically responsible person at Richmond Pharmacology is Dr Thomas Ashdown (Richmond Pharmacology Associate Medical Director) whose contact details are:

Dr Thomas Ashdown t.ashdown@richmondpharmacology.com 0207 042 5800

11. Privacy and confidentiality

Will my taking part in the clinical trial be kept confidential?

Yes. By signing this form, you consent to the Research Doctor and his/her staff at Richmond Pharmacology, the Sponsor Orphalan, regulatory authorities, and the Ethics Committee collecting, storing, transferring, and processing your personal data, including the following: your date of birth, your sex, your race or ethnic origin, personal data on your physical or mental health or condition and any other personal data obtained during your participation in the clinical trial or as a result of any follow-up assessments. Please refer to Appendix 2 for more information.

What will happen to any samples I give?

Samples	Processing and Analysis	Retention
Blood and urine (safety) 	Processed and analysed by a laboratory within the UK on an ongoing basis during the clinical trial. These samples will not have your personal details on them; however, they will be coded in a way that is linked to you (see Appendix 2).	These samples will be retained for a maximum of three months to perform all tests described in the clinical trial protocol, after which they will be destroyed.
Blood for pharmacokinetics 	Processed and analysed by a laboratory within the EU on an ongoing basis during the clinical trial. These samples will not have your personal details on them; however, they will be coded in a way that is linked to you (see Appendix 2).	These samples will be retained until the clinical trial has been closed to perform all tests described in the clinical trial protocol, incl. e.g., inspection related confirmatory re-analysis, after which they will be destroyed.

The samples will not be used for any other research that you have not consented to on this form.

Please contact the Research Doctor at any time if you require more detailed explanations about this.

12. Who has reviewed this clinical trial?

The protocol has been produced by Richmond Pharmacology and reviewed by Orphalan SA. This clinical trial has been approved by the **Medicines and Healthcare Products Regulatory Agency** (MHRA) which is the regulatory authority in the UK.

To protect your interests the clinical trial has been looked at by an independent group of people called a **Research Ethics Committee**. This clinical trial has been reviewed and given a favourable opinion by NRES Committee Berkshire B Ethics Committee (IRAS ID: 1009060).

This clinical trial is regulated by both national and international guidelines. Richmond Pharmacology Ltd is under the inspection of the MHRA ensuring that the quality of our clinical trial is to acceptable standards. According to Good Clinical Practice (GCP) guidelines, UK law and other relevant legal, regulatory, and scientific guidelines your clinical trial data must be stored and made accessible for at least 25 years after either drug development stops OR after the last approval of a marketing authorisation in a country where GCP applies. Results of the trial will be published on clinicaltrials.gov within 1 year of the trial finishing. For further information, please contact Richmond Pharmacology on the details above.

Thank you for considering taking part in this clinical trial.

RPL Number: <INSERT VDB LABEL>

Screening Number:

Informed Consent Form

Clinical Trial Title: A Phase I, Single Centre, Randomised, Interventional, Open-Label, Cross-Over Study to Evaluate the Pharmacokinetics (PK) and the Safety and Tolerability of a Total Daily Dose of 900mg of TETA 4HCL, Comparing a New Once Daily TETA 4HCL Formulation (300mg) (3x300mg Trientine Base Tablets, OD) with the Current Marketed Cuprior® Formulation (150mg) (3x150mg Trientine Base Tablets, BD) in Adult Healthy Male and Female Participants

Please read the following statements and put your short signature in the box to show that you have read and understood them and that you agree with them.		**Please provide short signature in each box**
1	I confirm that I have received verbal information on the above clinical trial, and I understand and have read the Participant Information dated 17/Jan/2024, Version 3.0 and have had the opportunity to ask questions and any questions I asked have been answered to my satisfaction.	☐
2	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. I am aware of any risks associated with withdrawal from the clinical trial before the end.	☐
3	I understand that sections of any of my medical notes and clinical trial-specific records may be looked at by responsible individuals from the sponsor or from regulatory authorities where it is relevant to my taking part in the clinical trial. I give permission for these individuals to have access to my records.	☐
4	By signing this consent form, I agree that my personal data, including photographs (this would only be applicable when monitoring possible side effects and will be taken in such a way as to prevent disclosure of my identity) and data relating to my physical or mental health or condition, and race or ethnic origin, may be collected and processed as described in the information sheet for the clinical trial.	☐
5	I acknowledge that some of my samples may be sent outside the UK for analysis; where they have data protection laws which may be different than what is found in the UK; and I accept that the transferred samples will not be covered under the Human Tissue Act (the laws that govern and protect the collection, storage, use and disposal of human tissue in the UK).	☐

RPL Number: <INSERT VDB LABEL>
Screening Number:

6	I give my consent for my General Practitioner (GP) to be contacted and informed of my participation on the clinical trial and of any significant, abnormal results seen at screening or during the clinical trial.	☐
7	I understand I will receive a copy of this Participant Information/Informed Consent Form.	☐
8	I understand that the general outcome and results of this clinical trial, will be posted to clinicaltrials.gov within 1 year of this trial finishing.	☐
9	I confirm that I voluntarily consent to participate in this clinical trial.	☐

RPL Number: <INSERT VDB LABEL>
Screening Number:

Participant:

The Research Doctor supervising this clinical trial has given me an explanation of the nature, purpose and likely duration of the clinical trial, and what I will be expected to do. I have also been advised about any possible discomfort and ill effects on my health or well-being which may result from my participation.

I understand that if I withdraw from the clinical trial at any time and for any reason, the information that I have provided will be kept and will continue to be used, transferred, and processed.

I have been given the opportunity to question the Research Doctor on all aspects of the clinical trial and have understood the advice and information given to me. I understand that the information for participants in its current **version number 3.0 dated 17/Jan/2024** which has been handed out to me forms part of this written informed consent.

Signature of Participant	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|:|__|__|

Observer:
Observer to signature of the participant and to the fact that they have read the document and freely given their consent.

Signature of Observer	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__||__|.|__|__|__|.|__|__|__|__|	|__|__|:|__|__|

Research Doctor:
I confirm that I have explained to the participant the nature, purpose, and possible hazards of these procedures, and therefore sign on behalf of Richmond Pharmacology.

Signature of Research Doctor	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|:|__|__|

Richmond Pharmacology Limited | 1a Newcomen Street | London Bridge

SE1 1YR | Tel: 02070425800

Appendix 1 – What to do if there is a problem

1. If you suffer any side effects or injury, notify the Research Doctor immediately so that you can receive appropriate medical treatment.

2. If you suffer injury caused directly by participation in the clinical trial, the sponsoring company Orphalan SA will pay you compensation in accordance with the Association of British Pharmaceutical Industry Clinical Trial Compensation Guidelines 2014 [*compensation_guidelines_2014.pdf (abpi.org.uk)*]. A copy can be provided to you.

3. Any dispute or disagreement as to the application of clause 2 and above shall be referred to an arbitrator to be agreed between yourself and the sponsor. If you and the Sponsor cannot agree on the identity of an arbitrator, the President of the Royal College of Physicians of London will be invited to appoint an arbitrator with the power to consult a barrister of 10 years standing on any issue of law including the amount of damages to be paid.

4. The agreement to pay compensation shall be construed in accordance with English law and subject to the clause 3 above, the English courts shall have sole jurisdiction over any dispute which may arise out of it.

5. You are not being asked to give up any of your legal rights by agreeing to take part in this clinical trial.

Both Richmond Pharmacology and Orphalan SA have insurance policies in place for insuring against claims for their alleged liability.

Appendix 2 – Use of Personal Data

How will we use information about you?
We will need to use information from you, from your medical records, and your GP for this research project.

This information will include your Initials,

- NHS number,
- Name,
- Contact details,
- Medical/health information,
- Year of birth,
- Race and ethnicity,
- Demographic information,
- Back-up family/emergency contact details.

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Some of your information will be sent to France. They must follow our rules about keeping your information safe. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

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

You can find more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- on the HRA leaflet available from www.hra.nhs.uk/patientdataandresearch OR a printed version can be provided.
- by asking one of the research team
- by sending an email to DPO@richmondpharmacology.com (Site's Data Protection Officer), or (dataprivacy@orphalan.com)
- by ringing us on +44 56 0375 0073 (Sponsor's Data Protection officer).