Imperial College London

NHS
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NHS Trust

Information Sheet for research cerebral small vessel disease (cSVD) participants in the randomisation phase

Study Title:	**Targeting 18kDa Translocator Protein (TSPO) to improve brain endothelial cell function in cerebral small vessel disease**
Sponsor:	**Imperial College London**
IRAS ID:	**339664**

Chief Investigator:	**Prof Paul Matthews**
Principal Investigator:	**Dr David Owen**

Introduction

We invite you to take part in our research study, which investigates whether taking a drug called XBD173 will improve the function of endothelial cells lining the brain's blood vessels, in people with cerebral small vessel disease (cSVD). Thank you for reading this information sheet.

Taking part in this study is entirely voluntary. Before you decide, it is important to understand why the research is being done and what it will involve. We urge you to discuss this study with our clinical study team members and your GP to answer any questions you may have. Please speak to your family and friends and take your time in making a decision. If you participate, you are required to sign the relevant informed consent form. Please ask us if there is anything that is not clear or if you would like additional information.

If you have medical insurance, please review the terms of the insurance policy and its restrictions carefully, since the participation in a clinical study may interfere with the terms of the policy you have. If applicable, you may wish to discuss this with your insurance company.

What is the purpose of this study?

Cerebral small vessel disease (cSVD) affects the smaller blood vessels in the brain. Damage to the 'endothelial cells' which form the inner lining of the blood vessels are part of the cause of cSVD. The purpose of this study is to test whether a drug called XBD173, which targets a protein in blood vessels called Translocator Protein (TSPO), can modify the damage of endothelial cells and increase blood flow to the brain when the brain is active.

Who is organising and funding the research?

The research is organised by Imperial College London (Sponsor) and funded by UK Dementia Research Institute (DRI). The Chief Investigator is the former head of the Imperial DRI and is currently a group leader within the Imperial DRI. Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for their role in the research study.

Why have I been invited?
We are recruiting up to 76 patients with cSVD.

Do I have to take part?

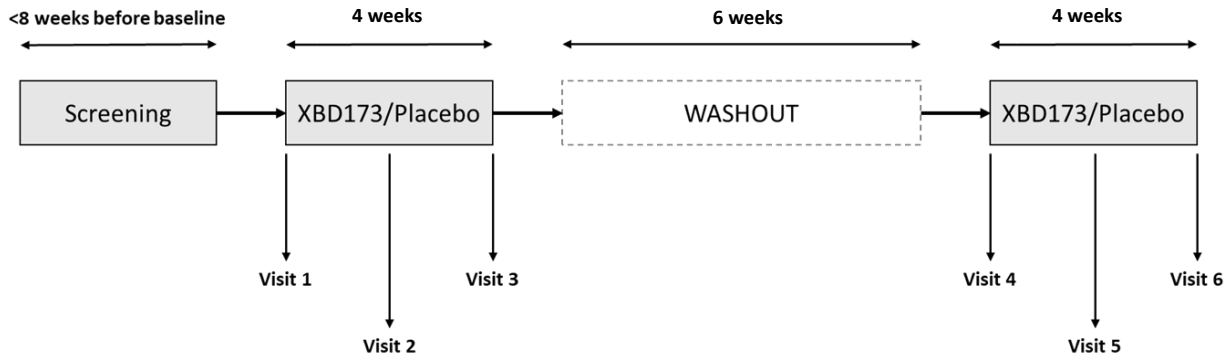
No. It is up to you to decide whether you wish to join the study. You are free to withdraw at any time, without giving a reason. Deciding not to take part or to withdraw at any time will not affect the standard of the NHS care that you receive.

Are there any people who should not enter the study?
There are some medications that should not be given with XBD173. We will check whether you take these medications, and we will not enrol you if you do. For your reference, the medications that should not be taken with XBD173 are at the end of this information sheet (page 13). We kindly ask you to inform the research team if you commence any new medications during the study.

What will happen to me if I decide to take part?

Participants will be given either XBD173 (90mg, twice daily) or a placebo (dummy drug) for 4 weeks. They will then have 6 weeks off, and then switched to the other treatment for 4 weeks. The XBD173 and placebo look the same, and so you will not know whether you are given the XBD173 first or the placebo first. The study team will not know either.

Study Design Schematic



●Before your first visit
This section is relevant to those participants who have contacted us via a study advert. When you first get in touch with us, a member of the research team will have an informal telephone conversation with you to tell you more about the study and answer any questions you may have. There is no commitment to take part at this stage. With your permission, and before asking you to come in for a

visit, we would like to do a few checks to make sure the study is likely to be suitable for you. This would save you an unnecessary trip if it turns out you are not eligible. Specifically, we would like to:

- Contact your hospital or GP to review your brain scan and report
- Obtain a recent clinic letter confirming your diagnosis and medications

We will only do any of these things if you agree. After your initial call with us, we will send you an email explaining exactly what we are asking permission for. If you are happy to proceed, simply reply to confirm. You do not have to agree, and saying no will not affect your care in any way. These checks are optional and will not be needed for everyone before a formal screening visit is arranged. If these checks suggest you are likely to be eligible, we will invite you in for a formal screening visit. At that visit, we will go through the study in full, answer any further questions, and ask you to sign a consent form before anything else happens. If the checks suggest the study is not suitable for you, we will not keep the brain scan images, report or GP summary. We will let you know the outcome and, where appropriate, suggest you speak to your usual clinical team. In order to obtain the information required, we will need confirmation of some of the following details: full name, date of birth, NHS number and GP details.

● Informed consent

Before you can start the study, a member of the clinical study team will talk to you in detail about the study. If you decide to participate, you will be asked to sign the informed consent form before any study procedures are done. You will be given a copy of this information sheet and the signed and dated consent form. Another copy will be sent to your GP. The originals will be kept at the research site.

● Screening assessment

This appointment may take up to 2 hours and will take place at the NIHR Imperial Clinical Research Facility (ICRF) on the Hammersmith Hospital site of Imperial College Healthcare NHS Trust. Your eligibility will be confirmed using data collected on the day. In more detail, at this assessment we will:

- obtain written informed consent
- confirm you meet the requirements to take part in the study
- record demographics (ethnic background, gender, age)
- ask about your medical and medication history (incl. smoking and alcohol history)
- perform a standard physical examination
- record your vital signs: (i) blood pressure, (ii) heart rate, (iii) temperature, (iv) oxygen saturation (incl. breathing rate), (v) height, and (vi) weight
- obtain blood samples for haematology, clinical chemistry and coagulation
- obtain blood samples for genetic tests for the TSPO gene and the ApoE gene
- trial of carbon dioxide administration (breathed in through an oxygen mask)

● Study visits 1, 3, 4 & 6

These study visits will take place at the NIHR ICRF and the Robert Steiner Unit, Imperial College London, Hammersmith Hospital campus, and are spread out over 14 weeks. Each one will take up to half a day. All the study visits are very similar, and all involve the following:

- a medical history and examination
- documentation of medications you are taking

- extended baseline cognitive test (visits 1 & 4 only)
- record your vital signs: (i) blood pressure, (ii) heart rate, (iii) temperature, (iv) oxygen saturation (incl. breathing rate), (v) height, and (vi) weight
- obtaining venous blood samples
- venous cannula placement
- MRI scan with alertness task, gadolinium contrast and carbon dioxide administration (at the Robert Steiner Unit)
- blood vessel function tests (this involves inflating cuffs as though as you are having blood pressure measured and putting a probe on your fingers as though you are having oxygen levels monitored)

An MRI safety checklist will be conducted at the screening assessment and verified by the imaging staff at the Robert Steiner Unit at the study visit.

N.B. On the morning of your study visits, please refrain from caffeinated drinks, fizzy drinks, heavy exercise, and high carbohydrate meals for 2 hours before your arrival. This is to make sure your test results are accurate.

There are some differences between the study visits:
- Study visit 1 will involve the first dose of the study drug XBD173 **or** placebo
- Study visit 4 will involve the first dose of the other

● **Study visits 2 & 5**

These are safety visits which will take place at the NIHR ICRF following the start of either treatment. These will be shorter visits and involve the following:
- a medical history and examination if required
- review of inclusion/exclusion criteria
- obtaining venous blood samples

Starting the XBD173/Placebo
On study visit 1, once all the procedures have finished, you will be given the first dose of the study drug (XBD173) or placebo to take. You will be given more capsules (XBD173 or placebo) to take home We will ask you to take one capsule in the morning and one capsule in the evening (e.g. at breakfast and dinner). Ideally, the capsules should be taken approximately 12 hours apart. You are kindly asked to fill in two paper records (provided by us): a medication record to monitor the times you are taking the study drug and a participant diary to record any new symptoms or medications during the study. Please take the study drug at approximately the same time each day and note the details in the record.

If you forget to take a dose of the XBD173/Placebo
If you forget to take a dose of the study drug and it is less than 4 hours late, take the missed dose as soon as you remember. If it has been more than 4 hours since the capsule was due, omit that dose and continue to take the next capsule as usual. Please record any late or missed doses in the diary provided.

Stopping the XBD173/Placebo

After 4 weeks (28 days), you will take your final capsule of XBD173/Placebo. At this visit, please bring any unused capsules with you so we can dispose of them.

Washout period
After taking your assigned treatment for 4 weeks, there will be a minimum 6-week break of no treatment (washout period). After 6 weeks, you will be assigned to the other drug for another 4 weeks in the exact same manner as for the first (twice a day). You will be asked to maintain a record to monitor the times you are taking the drug. Again, at the end of the second 4-week block, you will be asked to bring any unused capsules for disposal.

What is the drug that is being used?

XBD173 is a drug which was initially developed by the pharmaceutical company Novartis to treat anxiety. XBD173 was very well tolerated but Novartis stopped development of XBD173 because it did not reduce anxiety in their clinical study. We cannot ensure that the study drug will not have any side effects in this study but you will be closely monitored throughout.

What are the possible benefits of taking part?

You will not gain any personal benefit from this research. However, information from this study could improve our understanding of cerebral small vessel disease (cSVD) and help doctors to treat patients better in the future.

What are the possible disadvantages, risks and side effects when taking part?

● Side effects from the XBD173
XBD173 is not licensed as a treatment for any disease or condition. It is not prescribed by doctors to treat patients. Therefore it has not been given to many people. When XBD173 has been given to healthy volunteers in earlier studies once a day for 7 days, the most common side effects were abdominal symptoms and nervous system disorders (such as headache). However, these symptoms were not severe, and were just as common in volunteers in the same study who only received a placebo (dummy drug) instead of XBD173. In this study you would be taking XBD173 **twice a day for 28 days**. As with all drugs, you could experience side effects. These could affect any part of the body, but most commonly affect the liver, kidney, or blood cells. We will take blood tests every two weeks to identify any of these side effects as early as we can. It is also important you tell us if you notice any symptoms.

● MRI (Magnetic Resonance Imaging)
The MRI scanner contains a very strong magnet. You may not be able to have the scan if you have any type of metal implanted in your body, for example a heart pacemaker. A member of the team will ask you questions about this before you have the MRI. There is not much room inside the scanner. Some people may be uncomfortable if they do not like to be in enclosed spaces. You will be closely monitored and have contact with a researcher at all times. You may hear a hammering noise during part of the procedure. You will be given ear plugs and headphones to prevent discomfort or damage to your hearing. The headphones will also allow you to hear us talk to you. You should not experience any discomfort. We will give you an alarm bell to sound at any time if you are upset or worried. If the procedure does not suit you for any reason it can by stopped at any time. **We will place a cannula**

in one of your veins. A cannula is a small plastic tube which will allow us to give you a dye during the scan so we can measure blood flow.

● Venous cannulation
The contrast agent (dye) is called gadolinium and is routinely given to patients undergoing MRI. Insertion of a cannula (small plastic tube) into a vein feels like a sharp scratch and may take more than one attempt. It may leave a bruise afterwards. There is a small risk of the contrast leaking (extravasation) outside the vein which may cause swelling and discomfort. Uncommonly the contrast injection can cause people to feel nauseous or be sick. It is rarely associated with allergic reactions and breathing difficulties which require hospital treatment. Nephrogenic systemic fibrosis (NSF) is a serious complication associated with some contrast agents in patients with severe kidney disease. We will check that your kidney function is normal before you take part in the study. Trace amounts of gadolinium may stay in the body long-term. Available information does not identify any adverse health effects.

● Carbon dioxide administration
This scan tests how well the brain blood vessels can open up and increase blood supply to the brain when needed. During the MRI brain scan you will wear an oxygen mask over your nose and mouth. We will give you air to breathe that has a low amount of carbon dioxide, a gas that occurs naturally in the air, added to it. This should make the blood vessels open up which we can measure on the scans. The technique has been used in many hospitals around the world. A member of the clinical study team will be present during the brain scans and they will be monitoring your breathing, pulse and oxygen levels whilst you breathe the gas. This lasts around 15 minutes.

Most patients find the oxygen mask and air with carbon dioxide easy to tolerate. Some people feel that their breathing is a little harder, like during exercise. A few people feel that the mask is uncomfortable and makes the scan feel more claustrophobic. To minimise this, we keep the mask on for as little time as possible (15 minutes in the MRI scanner) and you are given a button to press if you want the scan to stop at any time.

You will be given a trial of carbon dioxide administration during the screening assessment, and if you are not able to tolerate it, you will still be able to enrol on the study if you are otherwise eligible.

● Blood tests
Routine blood sampling may cause pain, bruising or infection at the site where the needle/cannula (small plastic tube) enters your body. It is also possible that you may feel lightheaded or faint. Please let the clinical study team know if you do not feel well after having your blood taken. Over the course of the 14 weeks, approximately 200mL of blood will be collected as part of safety and research testing.

● Pregnancy
The effect of XBD173 on a human foetus (unborn baby) is unknown. This study is only recruiting women who are “postmenopausal”. A “postmenopausal state” is defined as no period for 12 months without an alternative medical cause. For this study, a man is considered fertile after puberty unless his medical notes state that he is permanently sterile. Fertile men are eligible to participate if they are willing to use the contraception methods with their partner listed below during the study, and for 90 days after the last dose of the study drug.

Highly effective contraceptive methods with typical-use failure rate <1% i.e. per year, when used consistently and correctly. Such methods include:

- sexual abstinence

- intrauterine device (also called IUD)[1]
- intrauterine hormone-releasing system (also known as IUS)[1]
- tubal ligation[1]

[1]*Contraception methods that in this context are considered to have low user dependency.*

What happens if my partner becomes pregnant during the study?

If you are male and your partner becomes pregnant during the study, one of the clinical study team would ask to talk to you regarding potential risks to your unborn baby. You will be requested to inform a member of the clinical study team of the outcome of the pregnancy and the health of the baby up to 8 weeks of age. We would ask you for your partner's contact details so we can invite them to the clinic for a discussion.

What if new information becomes available?

If new information regarding the study drug or procedures becomes available, we will tell you and discuss whether you should continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue, we may ask you to sign an updated consent form. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

During your participation, we might identify a previously undiagnosed illness or detect something which is abnormal and potentially clinically significant (known as an 'incidental finding'). We would inform you as soon as possible and discuss the implications and options available. With your consent we may refer you back to your GP or another clinician for follow-up, if appropriate. As a result of incidental findings you might need to be withdrawn from the research study, but we would discuss this with you.

If a possible malignancy (cancer) is detected on brain scans, your images will be reviewed by a multi-disciplinary team of NHS experts who will attempt to make a diagnosis and recommend a plan for treatment. This is done automatically to ensure that it is dealt with urgently, and may happen even before we have been able to contact you.

It is important to us that you are fully informed so that you can make decisions for yourself about taking part in this study. We will do our best to communicate with you openly and clearly, so please ask questions at any time if there is anything that you are unsure about.

What happens when the research study stops?

Once the study is completed, we will prepare a summary in lay language which will be circulated to those expressing interest. Please tell us if you would like to receive this summary.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr David Owen d.owen@imperial.ac.uk). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team

Will my doctor be informed about the study?

A letter will be sent to your GP informing them of your participation in the study. Any relevant clinical findings will be shared with them.

What will happen to any samples I give?

All samples will be labelled with a code. This will remove your identity and ensure you will not be identifiable through your sample to any of the researchers who use your samples. Blood samples collected for routine tests will be analysed in your local hospital laboratory. Samples collected for gene and research analysis will be securely stored at Imperial College. Any clinical data shared by researchers will be pseudonymised (coded). For selected measurements, a small quantity of each sample may be processed in a laboratory overseas (e.g. in Europe or in the USA). Any data shared with these third parties will be pseudonymised, ensuring that they are unable to identify you. With your permission, we will continue to store any remaining blood samples securely for use in related studies by our group for up to 10 years. Future studies will be subject to further ethical approval(s).

What will happen if I lose the capacity to consent during the study?

If you lose the capacity to consent during the study, you will be withdrawn from the study. Identifiable data or blood already collected will still be used in the study. However, no further data or blood will be collected, and no other research procedure will be carried out.

What will happen to the results of the research study?

The results of this study will be used in fulfilment of a PhD degree and will be published in peer-reviewed academic journals, conference presentations, and internal reports. They will be also presented locally, as well as at national and international meetings and congresses. Please be reassured that you will not be identified in any report or publication.

Expenses and Payments

You will receive £420 for taking part in this study to compensate you for your time and to cover travel expenses. The payment will be made at the end of the study, by direct payment into your bank account Your name, address, subject ID, age, email address, and mobile phone number may be collected and given to the local finance department to manage this payment. Your personal information will be stored on a confidential computerised processing system and will not be shared with any third parties. Your personal information will be kept completely confidential. If you need a carer to accompany you to the research site, their reasonable travel and subsistence costs will also be reimbursed.

In the event, that you undergo screening and are not eligible to participate in the study, you will be reimbursed £60. If you decide to withdraw from the study, you will be reimbursed at a pro-rata rate of £60 for each study visit.

Who has reviewed the study?

This study has been reviewed by a Research Ethics Committee - a group of people separate from your doctor, whose primary concerns are the safety, rights and welfare of participants in this study. This study has been reviewed and given a favourable opinion by the West London & GTAC Research Ethics Committee (Ref. 24/LO/0540), and the Health Research Authority (IRAS ID: 339664)

Contact for further information:

Please ask any questions now that you wish to. A copy of this information and of the consent form will be given to you to keep. If any questions occur to you later, or you have other concerns or would like to discuss any aspect of the study, please contact one of the following persons:

For management/operational issues please contact:

Daisy Metcalf, Co-Investigator and Physician Assistant
Imperial College London, Hammersmith Hospital,
NIHR Imperial CRF, Du Cane Road, London W12 0HS
E-mail: daisy.metcalf@nhs.net
Tel : 0203 313 6189

If you wish to send a complaint, please contact:

Dr David Owen, Principal Investigator
Imperial College London, Hammersmith Hospital,
NIHR Imperial CRF, Du Cane Road, London W12 0HS.
E-mail: d.owen @imperial.ac.uk
Tel: 0203 313 6195

Robert Steiner Unit contact:

Ben Statton, MR Facility Manager

Imperial College London, Hammersmith Hospital
Du Cane Road, London W12 0HS
Tel: 0208 383 3034

You may also wish to contact the local NHS Patient Advice and Liaison Office (PALS): 020 3312 7777 or imperial.pals@nhs.net

How will we use information about you?

Imperial College London is 'the Sponsor' for this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

For more information / confirmation regarding the end date please contact the study team, see 'WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED' for contact information.

The study is expected to finish in January 2028

We will need to use information from you, from your medical records and/or your GP for this research project. This information includes your:

- Initials
- Name
- NHS number
- Contact details
- Date of birth

People within the College and study team (see section sharing your information with others) will use this information to do the research or to check your records to make sure that the research is being done properly and the information held (such as contact) details is accurate. 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. 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.

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

• Imperial College London - "performance of a task carried out in the public interest"); Health and care research should serve the public interest, which means that we have to demonstrate that our

research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

Where special category personal information is involved (most commonly health data, biometric data and genetic data, racial and ethnic data etc.), Imperial College London relies on "scientific or historical research purposes or statistical purposes

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the United Kingdom (for example, to a research partner, either within the European Economic Area (EEA) or to other countries outside the EEA. Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a UK adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient research partner that incorporates UK approved standard contractual clauses or utilise another transfer mechanism that safeguards how your personal data is processed.

SHARING YOUR INFORMATION WITH OTHERS

We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

- Other Imperial College London employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.), Imperial College London agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.
- Study data will be shared with research collaborators at the University of Manchester for analysis purposes. Any data shared between researchers will be pseudonymised (coded), ensuring that they are unable to identify you.

POTENTIAL USE OF STUDY DATA FOR FUTURE RESEARCH

When you agree to take part in a research study, the information collected either as part of the study or in preparation for the study (such as contact details) may, if you consent, be provided to researchers running other research studies at Imperial College London and in other organisations which may be universities or organisations involved in research in this country or abroad. Your information will only be used to conduct research in accordance with legislation including the GDPR and the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you, used against you or used to make decisions about you.

COMMERCIALISATION

Samples / data from the study may also be provided to organisations not named in this participant information sheet, e.g. commercial organisations or non-commercial organisations for the purposes of undertaking the current study, future research studies or commercial purposes such as development by a company of a new test, product or treatment. We will ensure your name and any identifying details will NOT be given to these third parties, instead you will be identified by a unique study number with any sample / data analysis having the potential to generate 'personal data'.

Aggregated (combined) or anonymised data sets (all identifying information is removed) may also be created using your data (in a way which does not identify you individually) and be used for such research or commercial purposes where the purposes align to relevant legislation (including the GDPR) and wider aims of the study. Your data will not be shared with a commercial organisation for marketing purposes.

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, because some research using your data may have already taken place and this cannot be undone.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital and/or your GP. If you do not want this to happen, tell us and we will stop. This will not affect any healthcare or support you may be receiving separately

• 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 if this could affect the wider study or the accuracy of data collected.

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

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

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by ringing us on +44(0)2075943502.

Complaint

If you wish to raise a complaint about how we have handled your personal data, please contact the research team first by sending an email to d.owen@imperial.ac.uk, or by ringing us on 020 3313 8070. Following our response, if you are not satisfied please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and/or via post

at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ. If you remain unsatisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO)- via www.ico.org.uk. Please note the ICO does recommend that you seek to resolve matters with the data controller (us) first before involving them.

The medications listed below should not be taken during the study or during the 48-hours after the final dose of XBD173

- Boceprevir (Victrelis®)
- Clarithromycin (Klaricid®, Klaricid XL®, Xetinin XL®)
- Cobicistat (Tybost®), Idelalisib (Zydelig®)
- Itraconazole (Sporanox®)
- Ketoconazole (Daktarin Gold®, Dandrazol®)
- Nelfinavir (Viracept®)
- Ritonavir (Norvir®)
- Saquinavir (Invirase®)
- Telaprevir (Incivek®)
- Telithromycin (Ketek®)
- Voriconazole (VFend®)
- Aprepitant (Emend®)
- Conivaptan (Vaprisol®)
- Crizotinib (Xalkori®)
- Diltiazem (Adizem®, Angitil®, Tildiem®, Viazem®, Zemtard®)
- Dronedarone (Multaq®)
- Erythromycin (Erythrocin®, Erythroped®, Erymax®, Tiloryth®)
- Fluconazole (Azocan®, Diflucan®, Canesten Thrush Oral Capsules®)
- Imatinib (Glivec®), Isavuconazole (Cresemba®)
- Nefazodone (Serzone®, Dutonin®, Nefadar®)
- Netupitant (Akynzeo®), Nilotinib (Tasigna®)
- Posaconazole (Noxafil®)
- Tofisopam (Grandaxin®)
- Verapamil (Securon®, Verapress®, Varatil®, Vertab®)
- Delavirdine (Rescriptor®)
- Carbamazepine (Tegratol®, Curatil®)
- Enzalutamide (Xtandi®)
- Fosphenytoin (Cerebyx®, Sesquient®)
- Mitotane (Lysodren®)
- Phenytoin (Epanutin®)
- Rifampicin (Rifadin®, Rimactane®)
- Bosentan (Tracleer®)
- Efavirenz (Sustiva®)
- St John's wort
- Barbiturates e.g. Phenobarbital (Luminal®)
- Nevirapine (Viramune®)
- Primidone (Mysoline®)
- Rifabutin (Mycobutin®)
- Rifapentine (Priftin®)
- Oral contraceptives