Participant Information Sheet (PIS)

Trial title: STRATIFY lupus

A Phase IIIa randomised placebo-controlled biomarker enrichment trial: IgA2 anti-DNA antibodies as a biomarker of response to belimumab after rituximab in systemic lupus erythematosus

We want to invite you to join our trial. Your trial doctor thinks you might be able to take part. University College London (UCL) is the trial sponsor in charge of the trial. UCL must run the trial properly. A member of the trial team will go through this sheet with you. They will answer any questions you have. This should take around 20 minutes. You can also talk to family or friends. Take your time to decide if you would like to join the trial.

1. What is the purpose of this trial?

- The trial will see if it is better to treat lupus with:
  - Belimumab after rituximab **(RTX)** or
  - RTX on its own.
- Doctors give RTX to patients with active lupus. RTX removes a type of white blood cell called B cells. These B cells can cause disease in lupus patients by producing harmful antibodies which are proteins in the blood that can attack the body's own tissues, when they do these antibodies are called autoantibodies. Some patients respond well to RTX, but the disease can come back.
- The disease can return because of a chemical messenger in the body called BAFF. When treatment stops, BAFF levels can rise and cause lupus to become active again. Belimumab treats lupus patients with active disease and stops BAFF from working.
- STRATIFY lupus builds on an earlier trial called BEAT-lupus. The BEAT-lupus trial found that some people had fewer flare-ups from RTX and belimumab.
- Testing samples from BEAT-lupus found that a type of antibody in the blood called IgA2 anti-dsDNA antibodies were increased in patients who responded better to belimumab after RTX. IgA2 anti-dsDNA antibodies are a type of autoantibody in the blood.
- STRATIFY lupus trial is for people with high levels of IgA2 anti-dsDNA antibodies. By carrying out the STRATIFY lupus study for people with high levels of IgA2 anti-dsDNA antibodies, researchers will answer the question whether a higher number of people will respond to the combination of belimumab after RTX than RTX alone.

- The trial could help the treatment reach the people who need it most. We will recruit 66 people in total across the UK.

2. Why did you invite me?

Your trial doctor thinks this trial might be of interest to you, as you:

- have lupus that is active.
- your trial doctor has suggested you start RTX treatment.

3. Do I have to take part?

No. It is up to you to decide. If you choose not to take part, you may still get RTX. Your doctor will discuss this with you. Your choice will not affect your care.

4. What happens if I choose to take part?

Your trial team will explain the trial in more detail. They will answer any questions you have. The first visit is the screening visit (visit 1). Your trial team will do some tests. These tests are to see if you can take part. You can learn more about these tests on pages 14-17. This visit will take at least 1 hour. The aim of these checks is to:

- make sure you are well enough to have treatment. Your trial team will take and test blood and urine samples. If you are a person of childbearing potential, you will have a pregnancy test.
- check your lupus and how it is responding to treatment. Your trial doctor will talk to you about other medicines you take. You might need to safely stop or lower the dose for some of them.
- fill in forms. The forms will ask about how you are feeling. They will also see if you can do normal tasks.
- check for any side effects from lupus or treatment
- Check your blood for the IgA2 anti-dsDNA antibody to see if it is positive. Only patients who have a positive IgA2 anti-dsDNA antibody test can take part.
- Take extra blood, RNA (type of genetic tissue) and stool samples for research. You will collect stool samples at home. You do not have to give some of the samples. You can let your trial team know if you want to give them.

- The trial team will handle all samples with care. We will not store any personal details like your name or date of birth. We will do this before using the samples. There will be no health-related findings from the sample tests.
- The Rayne UCL lab will keep and look at the samples.

Not everyone will be able to take part. The trial team will let you know if you can join the trial. If you can, you will be randomly placed in **Group A** or **Group B**.

- **Group A:** Belimumab treatment for 48 weeks after RTX treatment.
- **Group B:** Placebo (saline) treatment for 48 weeks after RTX treatment.
- This trial is *'double blind'*. You and your trial team will not know which group you are in. Your trial team can find out in an emergency.
- The saline will look the same as the belimumab. It will not contain any medicine.
- Knowing your treatment can affect how you feel. This is why we use a placebo.

Each group will have 14 treatments over 52 weeks (12 months). **Treatment and Follow-up**

You will be in the trial for 12 months (52 weeks). At first, you will have treatment (infusions) every 2 weeks (visits 2-4, weeks 0-4). You will have treatment at the clinic or day-case unit. From visit 4 you will have treatment every 4 weeks. The last treatment will be at visit 15 (week 48). At your final visit (visit 16, week 52) you will not have treatment.

Each treatment takes between 1-3 hours. Your trial team will monitor you for safety. They can watch you for longer. You can find out about each visit at the end of this sheet.

5. Expenses and payments

You will be reimbursed for reasonable travel and other costs when you go to study visits. This can include things like public transport (bus, train or underground). This can include mileage if you use your own car (at standard NHS rates). Parking charges, taxi fares, a place to stay and food (if needed) can also be reimbursed.

You will need to show receipts to the trial team to be paid back. If you don't have a receipt (mileage or public transport), you will be paid based on NHS standard rates.

If you think your costs might be higher than usual, please tell your trial team. They will make sure you are not left out of pocket for joining this study. If a carer accompanies you for study visits, their expenses will also be reimbursed on the same basis as above.

6. Advantages and disadvantages of taking part

Advantages:

- Some people enjoy taking part in medical research. They enjoy the extra check-ups and contact with the trial team.
- The results from the trial could improve treatment for people with lupus.
- The results could teach us more about lupus.

Disadvantages:

- You might not benefit from taking part.
- This is a 'randomised double-blind' trial. This means a computer program will pick your treatment. You will not be able to choose or know which treatment you are on. After the trial ends, you can find out which treatment you had.
- The forms asking questions might include personal questions. You do not have to answer any questions you don't want to. Just tell your trial team.
- This trial collects stool samples. You do not have to give stool samples. You can withdraw consent at any time. Just let your trial team know.

7. What are the side effects of the trial medicine?

The table below shows the potential side effects of belimumab. There are some extra details about some of them. People in earlier studies reported these side effects. Belimumab might not have caused these side effects. These side effects can happen for other reasons like other treatments for lupus. If you have any side effects let your trial team know. You can find their contact details:

- At the end of this sheet.
- On the Trial Card.

How common is the side effect?	Side effect		
Very common (at least 1 in 10 people)	Bacterial infection e.g. bronchitis, urinary tract		
Common (up to 1 in 10 people)	High temperature (pyrexia)	Common cold (nasopharyngitis)	Nausea
	Migraine	Diarrhoea	Hypersensitivity reactions
	Depression	Low white blood cell count (leucopenia)	Hives (urticaria) or rash

	Viral upper respiratory tract infection	Infusion or injection-related systemic reaction	Pain in arms, legs, hands or feet
	intestinal infection (gastroenteritis viral)	Sore throat (pharyngitis)	Injection site reactions
Uncommon (up to 1 in 100 people)	Anaphylactic reaction*	Suicidal behaviour	Suicidal thoughts (ideation)
	Sudden swelling caused by allergic reaction (angioedema)		
Rare (up to 1 in 1000 people)	Delayed-type, non-acute hypersensitivity reaction		
Not known	Stevens-Johnson syndrome**	Toxic epidermal necrolysis	

*Anaphylactic reaction is a life-threatening allergic reaction that happens very quickly.

**Stevens-Johnson syndrome is a rare but serious skin reaction caused by taking certain medicines.

Serious Allergic reactions:

Some patients (up to 1 in 100 people) have a serious allergic reaction. These allergic reactions can be very serious but rarely cause death.

These reactions can cause:

- Swelling of face, lips, mouth or tongue
- Rash or itchy raised bumps (welts or hives)
- Wheezing
- High or low blood pressure
- Dizziness
- Finding it hard to breathe or shortness of breath
- Slow heartbeat

If you have any or all these, get medical help right away. Your Trial Card has the details of your trial team.

Your trial team might give you allergy medicine or other medicine before the treatment. Sometimes allergic reactions can happen after you've left the hospital. This can be 5-10 days after a dose of medicine. This can include any or all the symptoms listed above. Contact your trial team if you have any or all these symptoms.

Risk of infection:

Belimumab can make it easier for you to get an infection. Tell your trial doctor if you get

- chills

- a fever
- any other sign that makes you think you have an infection.

You should not have belimumab if you keep getting infections. Or if you find them hard to clear. If you have or keep getting infections talk to your trial doctor.

Progressive multifocal leukoencephalopathy (PML) is a serious and life-threatening brain illness. Your chance of getting PML can rise if you take medicines like belimumab. Tell your trial doctor right away if you have:

- memory loss.
- trouble thinking.
- it's hard to talk or walk.
- loss of vision, or similar problems.

Risk of cancer:

There is no data that shows belimumab raises the risk of cancer. But it is not certain that belimumab does not raise the risk of cancer.

Vaccines:

Vaccines help your body fight infections. Vaccines may not work as well if you get them while taking belimumab. Some vaccines might not be safe to take when you are taking belimumab. Make sure you double check with your trial team before taking any vaccines.

Pregnancy and Birth Control:

You cannot take part in this trial if you are:

- Pregnant
- breastfeeding
- planning to become pregnant within the next year.

Anyone who could become pregnant must agree to use a highly effective birth control. This must be from screening until at least 4 months after the last treatment. The trial team will report all pregnancies to the CCTU at UCL, and any pregnancies reported may be followed for up to 6-8 weeks after the delivery of your child to collect information on any ante- or post-natal problems. Examples of highly effective birth control:

- combined (oestrogen and progestogen containing) hormonal that blocks ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal that blocks ovulation:

  - oral
  - injectable
  - Implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised male partner
- sexual abstinence, defined as refraining from heterosexual intercourse (i.e., with male partner)

The effects of belimumab on pregnancy are not yet known or fully understood. This is also true for the developing foetus. You will have a urine pregnancy test at each visit.

If take mycophenolate (for example, CellCept®), you must use another method of birth control. This is unless you avoid sexual intercourse completely (abstinence as described above). You can discuss birth control with your trial doctor. Birth control pills might not work when you are taking mycophenolate.

Male fertility

Men do not need to use a highly effective form of birth control.

Serious mental health problems and suicide:

People with lupus sometimes have depression, suicidal thoughts, trouble sleeping, and anxiety. This includes people taking belimumab.

People with lupus who take belimumab may have depression or suicidal thoughts more often. This is rare.

If you:

- try to commit suicide.
- action dangerous impulses.
- have thoughts of suicide, hurting yourself or dying.
- feel depressed, worried or anxious.
- mood problems or changes in your behaviour.
- if family or friends have noticed any of the above. You may not agree with them.

You should:

- Go to your GP
- Contact 111
- Contact your trial team
- Contact a hospital

Go to page 13 for contact details for your trial team.

If you:

- have a serious suicide risk history
- have had suicidal behaviour in the last 6 months
- have had suicidal ideation in the last 2 months
- in opinion of trial doctor have high suicide risk

You will not be able to take part in the trial.

8. What happens when the trial stops?

Trials rarely stop early. If that happens, your trial team will explain the reasons to you. Your usual care outside the trial will go on.

If the trial ends early, you might be able to have belimumab. You must meet NHS rules:

- active disease. This is where your lupus symptoms get worse. You might get new symptoms or have more flares.
- usual treatments for lupus are not working as well.
- your SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment – SLE Disease Activity Index) score is 10 or more points. It must improve by 4 or more points after you get belimumab for 24 weeks (5 months).
- blood test that shows disease.

You should talk to your usual care team. If you meet the rules, they will arrange it.

10. What if there is a problem?

Every care will be taken during this trial. However, in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (University College London) or the hospital's negligence, then you may be able to claim compensation.

After discussing with your trial doctor, please make the claim in writing to Professor Michael Ehrenstein who is the Chief Investigator for the trial and is based at University College London (UCL). The Chief Investigator will then pass the claim to the Sponsor and on to the Sponsor's Insurers. If you have a claim, then it might be helpful to consult a lawyer.

Participants may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your trial doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the trial, the normal National Health Service complaints mechanisms are available to you. Please ask your trial doctor if you would like more details on this. Details can also be obtained from the NHS website.

[Please insert trial location's local PALs information]

11. What if relevant new information becomes available?

Sometimes during a trial, new details about the medicine can come out. If this happens and it might affect you, the trial team will tell you. You can discuss if you want to stay in the trial. The trial team might ask you to sign an updated consent form.

If you leave the trial for any reason your usual care won't change.

12. What happens if I don't want to carry on with the trial?

You are free to leave the trial at any time, for any reason. You will get the same standard of care. If you want to leave, contact your trial team. Their contact details are on page 13, and on the Trial Card.

You can stop the trial medicine but stay in the trial. We'll ask you to come to the rest of your visits. This is helpful to the trial. The final visit (at 52 weeks) is particularly important for the trial. We will keep your data and samples collected before you stopped. We will use them in the trial results. Please be aware that your right to erasure of personal data does not apply. This is because the data processed will be for research purposes. The research team will not publish any personal data.

You can leave the trial completely. We will keep your data and samples. We will use them in the trial results. Please be aware that your right to erasure of personal data does not apply. This is because the data processed will be for research purposes. The research team will not publish any personal data.

13. Will my taking part in this trial be kept confidential?

We will keep the data we collect from you strictly private. Your trial team will remove personal data.

Only approved people will access your data e.g. the sponsor Your GP practice will know that you are in the trial.

14. What will happen to the results of the trial?

- We will publish the results in a medical journal. We will write a summary of the results. Your trial team will send this summary to you within 12 months. Your trial team will also send you a link to the full results online.
- We will not publish any personal data. No one outside your trial team will know you took part.
- After the trial ends, you can find out which treatment you had.

15. Who has funded, organised and reviewed the research?

Arthritis UK and the NIHR fund the trial. A UCL team runs the research with help from UK experts. The CCTU at UCL runs the trial. CCTU will pay [insert trial location name] for your part in the trial.

A Research Ethics Committee has reviewed and approved the trial. So has the MHRA, who check all research that uses drugs. The Research and Development (R&D) department at your hospital has given approval.

Two Patient and Public Involvement Representatives have checked the trial documents. They make sure that all the sheet is clear and correct. These are people like you who have lived experience of lupus.

16. How will we use information about you?

We will need to use information from you and your medical records for this research project.

This information will include:

- Date of birth
- Ethnicity
- Gender
- Data about physical and mental health
- Data about your immune system obtained from the samples collected

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 details. Your data will have a code number instead.

UCL is the sponsor of this research and has given responsibility for the overall management of the trial to the CCTU at UCL. UCL is responsible for looking after your information. We will share your information related to this research project with the following types of organisations:

- academic
- regulatory
- charitable
- academic working with commercial

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

- making sure no personal data is shared with anyone outside of your clinical care team.
- limiting access to your data to only people doing the research. They will be confirmed to work on the trial.
- making sure all data about you, held physically or electronically, is stored and held securely.

Your stored samples may be used for future research but not for whole genome analysis, creation of cell lines or animal testing. This will only happen if you give separate consent.

International transfers

We may share or give access to data about you outside the UK for use in future ethically approved lupus research. This will only happen if you give separate consent.

If this happens, we will only share the data that is needed. We will also make sure you can't be identified from the data that is shared where possible. This may not be possible under certain circumstances. For instance, if you have a rare illness, it may still be possible to know who you are. If your data is shared outside of the UK, it will

be with the following sort of organisations:

- academic
- regulatory
- charitable
- academic working with commercial

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

- some of the countries your data may be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK.
- we use specific contracts approved for use in the UK which give personal data the same level of protection it has in the UK. For further details visit the Information Commissioner's Office (ICO) website: https://ico.org.uk/for-organisations/uk-gdpr-guidance-and-resources/international-transfers/
- we do not allow those who access your data outside the UK to use it for anything other than what our written contract with them says.
- we need other organisations to have appropriate security measures to protect your data. These will be consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your data against accidental loss and unauthorised access, use, changes or sharing.
- we have procedures in place to deal with any suspected personal data breach. We will tell you and applicable regulators when there has been a breach of your personal data when this is legally required. For further details about UK breach reporting rules visit the Information Commissioner's Office (ICO) website: https://ico.org.uk/for-organisations/report-a-breach.

17. How will we use information about you after the trial ends?

Once we have finished the trial, we will keep some of the data so we can check the results. The reports will be written in a way to make sure no one can know you took part.

We will keep your trial data for up to of 25 years. The trial data will then be fully anonymised and securely archived or destroyed.

What are your choices about how your information is used?

- you can stop being part of the trial at any time, without giving a reason, but we will keep information about you that we already have.
- if you choose to stop taking part in the trial, we would like to keep collecting information about your health from central NHS records, your hospital, or your GP. If you do not want this to happen, tell your trial team and we will stop.
- you have the right to ask us to access, remove, change or delete data we hold about you for the purposes of the trial. You can object to our processing of your data. We might not always be able to do this if it means we cannot use your data to do the research. If that is the case, we will tell you why we cannot do this.
- if you agree to take part in this trial, you will have the option to take part in future research using your data saved from this trial. The Rayne Building at UCL will store your data for 25 years.

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

- You can find out more about how we use your information, including the specific mechanism used by us when transferring your personal data out of the UK:
  - At www.hra.nhs.uk/patientdataandresearch
  - Our leaflet at https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/use-data
  - By asking one of the trial team
  - By sending us an email to data-protection@ucl.ac.uk

18. Further information and contact details

If you have any questions about the trial or your involvement, you can contact:

Local Principal Investigator:

- Trial Location PI Name
- Address
- Telephone
- Email
- Insert Trial Location's Emergency Contact Number

If you want to take part, please read and sign the consent form. You will be able to keep this sheet and your consent form. Your trial team will keep a copy of your consent form in your records. You can have more time to think this over if you are unsure.

Thank you for taking the time to read this sheet.

STRATIFY lupus visit summary		
Visit	**Event**	**Timeframe**
1st screening visit	Discuss the trial with your trial doctor and sign informed consent form. Check of past medical and surgical history. Check medicines. Vital signs. Physical exam. Blood and RNA samples taken. Stool sample done at home after visit. Pregnancy test for people who can become pregnant. Check of lupus symptoms and any side effects	
First RTX treatment within 7 days of screening visit		
Second RTX treatment two weeks after first RTX treatment as standard of care		
2nd screening visit (visit 1)	Medical and surgical history. Check medicines. Vital signs and weight. Physical exam. Blood samples taken. Pregnancy test for people who can become pregnant. Check of lupus symptoms and any side effects.	1 week before randomisation
Randomisation visit (visit 2)	Trial treatment (belimumab or saline). Check medicines. Physical exam. Vital signs and weight. Blood sampling for research and safety. RNA sample. Urine test.	1 week after your second screening visit

	Forms about lupus and how you feel. Pregnancy test for people who can become pregnant.	
Visit 3-4	Trial treatment (belimumab or saline). Check medicines. Physical exam. Vital signs and weight. Blood sampling for research and safety. Urine test. Forms about lupus and how you feel. Pregnancy test for people who can become pregnant. Check of lupus symptoms and any side effects.	Every 2 weeks
Visits 5-15	Trial treatment (belimumab or saline). Check medicines. Physical exam. Vital signs and weight. Blood sampling for research. RNA sample. Urine test. Forms about lupus and how you feel. Pregnancy test for people who can become pregnant. Check of lupus symptoms and any side effects.	Every 4 weeks
Visit 16 (last visit)	Check medicines, physical exam, vital signs, blood sampling for research, urine test, weight check. Forms about lupus and how you feel. Pregnancy test for people who can become pregnant. Check of lupus symptoms and any side effects.	4 weeks after visit 15