Participant Information Sheet (PIS)

Study title: STRATIFY lupus

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

We are inviting you to take part in our research study. You have been given this information sheet because your doctor feels you may be suitable to take part. University College London (UCL) is responsible for the study. Taking on this responsibility is called being the study sponsor. Before you decide if you would like to take part, one of your team will go through the information sheet with you and answer any questions you have. We suggest this should take about 20 minutes. Ask your team about anything that is not clear, talk to others about the study, if you wish, and take your time to decide whether or not you wish to take part.

1. What is the purpose of this study?

- The aim of the study is to investigate whether it is better to treat lupus by giving belimumab after rituximab compared to giving rituximab alone to lupus patients with raised levels of IgA2 anti-dsDNA antibodies. We will measure IgA2 anti-dsDNA antibodies from a blood test similar to the ones you have at your clinic visits.
- Rituximab is a treatment given to patients with systemic lupus erythematosus (lupus) who have active disease and works through removing a type of immune cell called B cells from the body. They can cause disease in lupus patients. Even though patients respond to rituximab the disease can quickly return.
- This is likely because of a chemical (also known as a stimulating factor) called BAFF which increases in the body when treatment ends and switches the lupus back on.
- Belimumab is a drug licensed and approved for use in people with lupus that have a high degree of disease activity and stops BAFF from working.
- STRATIFY lupus is based on a previous study called BEAT-lupus, which showed that some people with lupus who were treated with belimumab after rituximab had fewer severe lupus flares compared to when they were treated with rituximab alone.
- Samples from BEAT-lupus participants identified an autoantibody called IgA2 anti-dsDNA antibody. An autoantibody is a protein that is made by the immune system and can cause damage to the body.

- Research on IgA2 anti-dsDNA antibodies showed that this test could predict who will respond better to the combination of belimumab after rituximab.
- By carrying out the STRATIFY lupus study for people with high levels of IgA2 anti-dsDNA antibodies, researchers believe that a higher number of people will respond to the combination of belimumab after rituximab than rituximab alone.
- A positive study result may help to ensure access to this treatment combination for those people who are most likely to respond.
- STRATIFY lupus will aim to recruit 66 participants in total across the UK.

2. Why have I been invited?

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

- have lupus that is active.
- your doctor has recommended that you should be treated with rituximab for your lupus.

3. Do I have to take part?

No - it is entirely up to you to decide if you would like to join. If you decide not to, you will still receive rituximab (if you and your doctor decide this is best for you) and your decision will in no way affect the care you receive.

This information sheet will describe the study, and your study team will be able to go through this information with you. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw your consent at any time without giving a reason.

4. What happens if I choose to take part?

Your study team will explain the study in more detail and answer any questions you may have. At the screening visit (visit 1), your study team will check your eligibility by running a series of tests and assessments (see the listing provided at the end of this information sheet for more information). This visit will take at least 1 hour. The aim of these assessments is to:

- Check you are well enough to receive treatment by examining your blood and urine samples. If you are a person of childbearing potential, then you will have a pregnancy test.
- Assess the lupus and how it is responding to treatment. Your study doctor will discuss your other medications with you and decide which you should continue and at what dose as you may need to reduce the dose of some of your current medications. Your study doctor will discuss this with you and ensure this is done safely and appropriately.
- Complete questionnaires about how you are feeling and your ability to do everyday activities.
- Check for any side effects either from lupus or the treatment and take additional blood and stool samples (poo samples taken at home) for research. Some of these samples are optional and you can let your study team know if you wish to donate them or not.

Not everyone who is screened will be eligible to take part. The study team will contact you to let you know if you are eligible. If you are eligible and wish to continue, you will randomised (randomly allocated) to either **Group A** or **Group B**.

- **Group A:** Belimumab intravenous infusions for 48 weeks after rituximab treatment.
- **Group B:** Placebo infusions for 48 weeks after rituximab treatment.
- This study is *'double blind'* meaning neither you nor your study team will know which group you are in (although if your doctor needs to find out in an emergency they can).
- The placebo treatment will look identical to belimumab but with no active drug. Placebo is given to because sometimes knowing what treatment is given can affect the way a participant is feeling which can affect the results of the research.
- Participants from both groups will have a total of 14 infusions across the 52 weeks they are enrolled on the study.

Treatment and Follow-up

You will be enrolled in the study for 12 months (52 weeks). Initially you will have infusions every 2 weeks for visits 2-4 (weeks 0-4) at the clinic/day-case unit. From Visit 4 onwards, you will have infusions every 4 weeks until visit 15 (week 48, your final infusion).

Each infusion takes between 1-3 hours; the time can vary because your research team will want to monitor you after the first few infusions. They may monitor you for longer or for more than the first few infusions. The final visit (visit 6, week 52) will be 4 weeks after your final infusion. You can find details on the assessments and tests to expect at each visit in the listing provided at the end of this information sheet.

5. Expenses and payments

You will be reimbursed for travel and associated expenses up to £30 for each visit. Caring costs will also be considered for payment. Ask your study team for more information. There will be no other payment for participation in the study.

6. Advantages and disadvantages of taking part

Advantages:

- Some participants find it rewarding to take part in medical research and appreciate the additional monitoring and contact with the study team.
- The results from the study could potentially improve treatment for people living with lupus.
- The results from the study will increase our understanding of lupus.

Disadvantages:

- This is a 'randomised double-blind' study using a computer program and you will not be able to choose or know which treatment you are on. After the study is completed you can find out which treatment you received if you wish.
- The questionnaires may include sensitive or personal questions that you may not wish to answer. You do not have to answer any questions you don't want to. Your study team will support you in these instances.
- This study does collect stool samples– this is optional, and you can withdraw consent to the collection of these samples at any point during the study, just let your study team know.

7. What are the side effects of the study medication?

The table below details the potential side effects of belimumab with extra details on some specific ones. These are issues reported by patients in previous studies but may not actually be due to belimumab as they can occur for other reasons including other treatments for lupus you may be taking. If you have any side effects let your study team know, you can find their contact details at the end of this information sheet or on the Participant Study Card provided to you.

How common is the side effect?	Side effect
Very common (at least 1 in 10 people)	Bacterial infection e.g. bronchitis, urinary tract infection

Common (up to 1 in 10 people)	High temperature (pyrexia)	Common cold (nasopharyngitis)	Nausea
	Migraine	Diarrhoea	Hypersensitivity reactions
	Depression	Low white blood cell count (leucopoenia)	Hives (urticaria) or rash
	Viral upper respiratory tract infection	Infusion systemic reaction	Pain in arms, legs, hands or feet
	Inflammation of stomach and intestines (gastroenteritis)	Sore throat (pharyngitis)	
Uncommon (up to 1 in 100 people)	Anaphylactic reaction	Suicidal behaviour	Suicidal thoughts (ideation)
	Sudden swelling usually caused by allergic reaction (angioedema)		
Rare (up to 1 in 1000 people)	Delayed-type, non-acute hypersensitivity reaction		
Not known (can't be estimated from current data)	Stevens-Johnson syndrome	Toxic epidermal necrolysis	

Serious Allergic reactions:

Some patients (up to 1 in 100 people) have severe side effects due to an 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
- Difficulty to breath or shortness of breath
- Slow heartbeat

If you have any or all these serious allergic problems during the study, get medical help immediately. Your Participant Study Card has the details of your research team.

Your study team will monitor you closely during and after each infusion for any signs of a reaction. You may be given allergy medication or other medication like paracetamol before an infusion.

Sometimes allergic reactions can happen after you've left the hospital. This may happen 5-10 days after a dose of medication and can include any or all the symptoms listed above. If you experience any or all of these symptoms, please contact your study team.

Risk of infection:

Because of the type of medicine it is, belimumab may make it more likely for you to get an infection. Tell your doctor if you get chills or a fever or any other sign that makes you think you may have an infection. If you have an infection that keeps coming back or is hard to get rid of, you should not be treated with belimumab. Make sure you talk to your study doctor if you have or get these kinds of infections.

Progressive multifocal leukoencephalopathy (PML) is a serious and life threatening brain condition. Your chance of getting PML may be higher if you are treated with medicines that weaken your immune system, including belimumab. Tell your doctor immediately if you have memory loss, trouble thinking, difficulty with talking or walking, loss of vision, or similar problems.

Risk of cancer:

There has been no data to show that belimumab increases the risk of cancer in patients. However, it is not definite that belimumab does not increase the risk of cancer to a small degree.

Vaccines:

Vaccines help your body fight infections. Vaccines taken whilst being treated with belimumab may not work as well. There are also some vaccines that may not be safe to take when you are taking belimumab so make sure you double check with your study team before taking any vaccines.

Pregnancy and Contraception:

You will not be able to take part in this study if you are pregnant, breastfeeding or planning to become pregnant within the next year.

Anyone who is suitable to take part and can potentially become pregnant must agree to use a highly effective contraceptive or be sexually abstinent from the screening visit until at least 4 months after the last study treatment. All pregnancies will be reported to the Comprehensive Clinical Trials Unit at UCL (CCTU) and followed up appropriately.

The effects of the study treatment on pregnancy and developing foetus are not yet known or fully understood. At each visit you will be required to do urine pregnancy testing.

If you have lupus and are taking a drug for your lupus called mycophenolate (for example CellCept®), additional methods of birth control will be required unless you

avoid sexual intercourse completely (abstinence as defined above). Please discuss required methods of contraception with your study doctor. Birth control pills may not work as well when you are taking mycophenolate and you could become pregnant.

Male fertility

Male participants do not need to use a highly effective form of contraceptive or be sexually abstinent as rituximab and belimumab treatment has not been shown to have an effect to pregnancy outcome or foetal development.

Serious mental health problems and suicide:

Mental health problems, such as depression, suicide, trouble sleeping and anxiety have been reported in people with lupus including those receiving belimumab.

Depression, thoughts of suicide and attempting to commit suicide have been reported more frequently in people with lupus receiving belimumab although this is rare.

You can go to your GP, contact 111, your study team or the hospital if you:

- Attempt to commit suicide, action dangerous impulses or 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, even if you don't agree.

Go to page 12 for contact details for your study team.

8. What happens when the study stops?

It is rare that a study is stopped early. If this does happen, the reasons why will be explained to you by your study team and arrangements made for your usual care to continue.

If the study does not end prematurely, **once the study has ended it is possible you will have access to belimumab if you meet the NHS criteria (very active disease)**. You will need to discuss this with your study team.

10. What if there is a problem?

Every care will be taken during this study. 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 study doctor, please make the claim in writing to Professor Michael Ehrenstein who is the Chief Investigator for the study 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 study without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your study 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 study, the normal National Health Service complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the NHS website.

<< Please insert study location's local PALs information >>

11. What if relevant new information becomes available?

Sometimes during a study, new information becomes available about the treatment being studied. If this happens and the additional information has the potential to change your treatment options, the study team will let you know, discuss whether you want to continue in the study and you may be asked to sign an updated consent form.

If you decide to stop taking part or your study doctor suggests it is in your best interests to withdraw, your usual care will continue outside of the study.

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

You are free to withdraw from the study at any time, without giving any reason. The standard of your care will not be affected. If you wish to stop taking the study

medication **only** but are happy to continue to be followed up, we will ask you to attend the remaining study visits as it will be helpful for the study.

If you withdraw from the study or study treatment **only**, we will keep the information including samples we have already collected up to your withdrawal to use in analysis of the study results. Please be aware that your right to erasure of personal data does not apply because the data processed will be for research purposes, but no personally identifiable data will be published.

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

All information collected about you during the study will be kept strictly confidential and any information that leaves your study location will be pseudonymised, meaning that personal identifiers are removed/altered.

During the study only authorised people such as researchers, sponsors or regulatory authorities will have access to your data. The study team will inform your GP practice that you are taking part in the study.

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

- You will be given a summary of the findings within 12 months of the results being published.
- The results in full will be published in a medical journal for other doctors, healthcare professionals and researchers, this will also be available on the study website (link to website homepage will be inserted here when available).
- No identifiable information about you will be published so no one outside of your usual clinical team will be able to identify you or know that you took part.
- Once the study has ended you will be able to contact your study team and find out whether you received placebo or belimumab.

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

The study is funded by Arthritis UK and the National Institute for Health and Care Research (NIHR). The research has been organised by a team based at UCL with additional input from experts in the UK and is being managed by the CCTU at UCL who will pay [insert study location name] for the costs of including you in this study.

The study has been reviewed by an independent group called a Research Ethics Committee as well as the Medicines and Healthcare Products Regulatory Agency (who review all research involving drugs) and the study has been given a favourable opinion. The Research and Development (R&D) department at your hospital has also given permission for this study to happen.

The study documentation has also been reviewed by two Patient and Public Involvement Representatives. They will ensure that all the information is clear and accurate. These two individuals will be 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
- Information about physical and mental health
- Information 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 yourt details. Your data will have a code number instead.

UCL is the sponsor of this research and has delegated responsibility for the overall management of the STRATIFY lupus 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 organisations.
- Regulatory organisations.
- Charitable organisations.

- Academic organisations in collaboration with commercial organisations.

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

- Ensuring no personal identifiable information is shared with anyone outside of your clinical care team.
- Limiting access to your data to only researchers who are confirmed to be working on the study.
- Ensuring all information about you, whether held physically or electronically, is stored and maintained securely.

International transfers

We may share or provide access to data about you outside the UK for use in future ethically approved lupus research.

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 identify you. If your data is shared outside of the UK, it will be with the following sort of organisations:

- Academic organisations.
- Regulatory organisations.
- Charitable organisations.
- Academic organisations in collaboration with commercial organisations.

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 which are 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 study ends?

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.

We will keep your study data for a maximum of 25 years. The study 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 study 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 study, we would like to continue collecting information about your health from central NHS records, your hospital, or your GP. If you do not want this to happen, tell us 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 study. You can also 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 so, we will tell you why we cannot do this.
- 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. Your data will be stored at the Rayne Building at UCL 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 research team
  - By sending us an email to data-protection@ucl.ac.uk

18. Further information and contact details

If you have any questions regarding the study or how you might be involved further contact information can be found below.

Local Principal Investigator:

- <<Study Location PI Name>>
- <<Address>>
- <<Telephone>>
- <<Email>>
- Insert Study Location's Emergency Contact Number

If you decide you would like to take part, then please read and sign the consent form. You will be able to keep a copy of this information sheet and your consent form to keep. A copy of your consent form will be filed in your patient notes and study records. You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet.

STRATIFY lupus visit summary		
Visit	**Event**	**Timeframe**
1st screening visit	Discuss the study with doctor and sign informed consent form. Review of past medical/surgical history, medications, vital signs, physical exam, blood samples taken (optional stool sample done at home after visit) Pregnancy test for people who can become pregnant. Review of lupus symptoms and any side effects	
First rituximab infusion within 7 days of screening visit		
Second rituximab infusion two weeks after first rituximab infusion as standard of care		
2nd screening visit (visit 1)	Review of eligibility, medical/surgical history, medications, vital signs, weight, physical exam and blood samples taken. Pregnancy test for people who can become pregnant. Review of lupus symptoms and any side effects.	1 week before randomisation
Randomisation visit (visit 2)	Administration of study treatment (belimumab or placebo). Review medication, physical exam, vital signs, blood sampling for research and sampling, urine test, weight check. Questionnaires about lupus activity and how you feel.	1 week after your second screening visit

	Pregnancy test for people who can become pregnant.	
Visit 3-4	Administration of study treatment (belimumab or placebo). Review medication, physical exam, vital signs, blood sampling for research and sampling, urine test, weight check. Questionnaires about lupus activity and how you feel. Pregnancy test for people who can become pregnant. Review of lupus symptoms and any side effects.	Every 2 weeks
Visits 5-15	Administration of study treatment (belimumab or placebo). Review medication, physical exam, vital signs, blood sampling for research, urine test, weight check. Questionnaires about lupus activity and how you feel. Pregnancy test for people who can become pregnant. Review of lupus symptoms and any side effects.	Every 4 weeks
Visit 16 (last visit)	Review medication, physical exam, vital signs, blood sampling for research, urine test, weight check. Questionnaires about lupus activity and how you feel. Pregnancy test for people who can become pregnant. Review of lupus symptoms and any side effects.	4 weeks after visit 15