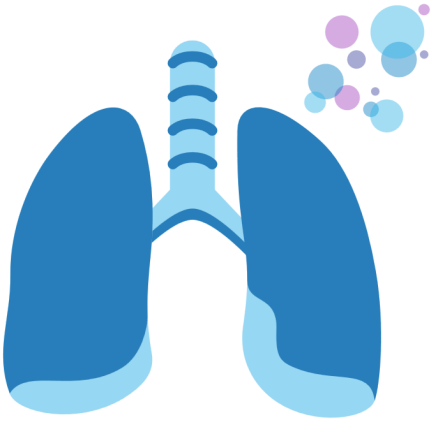
Participant Information Sheet (PIS)

Lung Immune Challenge Study:
Controlled Exposure to Inhaled Resiquimod (R848)
to Study Mechanisms of Inflammation



Lung Immune
Challenge Study

Key Details

Introduction

You are being invited to take part in this research study. Before you decide whether to join, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

We will tell you the purpose of this study and what will happen if you take part.

- **Key Details** about the study is explained first.
- The **Supplementary Information** at the end provides extra information.

Please feel free to ask the study team any questions you may have which are not answered in this information sheet. If you decide to take part in the study, you will be asked to sign a consent form and will receive a copy of this for your own records.

What is the background to the study?

Respiratory viral infections such as those caused by influenza or coronavirus can cause significant illness, especially in susceptible individuals. It is important to understand how the body's immune

system responds to these infections and how it differs between individuals. This understanding will help gain new scientific insights with the aim of developing new treatments.
The most relevant and direct way to study inflammation is by studying people (rather than just laboratory-based cell and animal models). This is because the scientific discoveries that are subsequently made are more likely to be successfully translated into the clinic, compared to relying on laboratory-based cell or animal models alone.

An established method of studying inflammation is through careful and controlled exposure (or "challenge") with a mimic of a virus to simulate an infection in a similar manner to that of a virus, but with the advantage of not causing disease.

We have already developed a mimic of human viral infection in the nose using a spray with a sterile substance called **Resiquimod** (also called **R848**). This does not contain any living organisms and therefore there is no possibility of becoming infected with this material.

Resiquimod works by interacting with cells that line the inside of the nose and lungs (epithelial cells) as well as cells that can fight infection (immune cells). These cells respond to Resiquimod resulting in short-lived inflammation, like what occurs with a mild cold. Researchers can then take samples to measure inflammation and investigate how it differs between individuals.

This helps us better understand how the human immune system responds to viruses, and which cells and molecules the body uses to defend itself. The recent COVID-19 pandemic also highlights the importance of this kind of research, as well as potentially being helpful for future pandemics.

What related research has taken place previously?

Resiquimod has been given as a **nasal spray** to 44 volunteers in previous studies at varying doses. It is well-tolerated in healthy participants and in those with asthma. Resiquimod has also been studied in clinical trials as a topical cream for the treatment of viral skin infections.

Therefore, Resiquimod can be used to mimic aspects of a viral infection in a way that is well-tolerated by volunteers and allows us to investigate and compare their immune responses.

What is the purpose of the current study?

Whilst Resiquimod has been given as a nasal spray, there are differences in how the nose and lungs respond to viral infections. This is especially the case in people with airway diseases such as asthma, who typically have epithelial and immune cells in the airways of their lungs that respond in a different way to inflammatory triggers (such as viruses) to other people. Therefore, there is a need to build upon the existing approach using nasal challenge with Resiquimod and develop a **lung immune challenge approach**.

The purpose of this study is to find out the best dose of Resiquimod to use in the lungs that causes a short duration of mild inflammation, whilst also ensuring that any symptoms caused are tolerable and acceptable for volunteers taking part in the study.

Once established, this will also be a more practical and easier method of studying immune responses in the lungs compared to other research studies which use live viral challenge approaches (for example with influenza). This is because live viral challenge studies are more difficult to perform as they are technically challenging, expensive and require volunteers to undergo quarantine for several days to prevent them causing infection in family members.

Therefore, an approach using inhaled Resiquimod instead would provide an easier, less complex, and practical method for investigating lung inflammation without causing an infection.

How will Resiquimod be given into the lungs and what will be measured?

Resiquimod will be given into the lungs in a very small volume (1 mL) using a **nebuliser**, which is a commonly used small machine that generates a fine mist. This mist can be gently inhaled via a mouthpiece into the lungs over a short period of a few minutes.

In order to assess whether inhaled Resiquimod generates an inflammatory response, participants will be asked to cough up phlegm **(sputum)** with the help of a salty water nebuliser ("induced sputum"), as well as provide **blood samples** from a vein. The study team will then measure inflammatory proteins in the sputum and blood to assess whether the dose of Resiquimod is sufficient to cause the expected response.

To ensure the safety of volunteers and collect data on symptoms, participants will be closely monitored with **measurement of vital signs** (e.g. pulse, blood pressure, oxygen levels), assessment of **airway function** (by blowing into a tube, termed "spirometry"), and asked to complete **questionnaires** describing any symptoms they may be experiencing.

How is the study designed?

The study will initially enrol healthy adults aged 18-60 (male and female) with no known asthma or other medical conditions. Later in the study people with asthma will also be enrolled.

To test which dose of Resiquimod is optimal, the study has been designed to have four dose groups with each group having 6 participants. Within each dose group, 4 participants will receive Resiquimod whilst 2 participants will receive saline. They will be randomly allocated (**randomized**) to either Resiquimod or saline and participants will not be aware of which intervention they are receiving. The study doctor will be aware of the group to which the participant has been randomised.

The reason for this study design is so the study team can compare responses between Resiquimod and saline to assess if Resiquimod causes the expected inflammatory response. It will also ensure that participants are able to report any symptoms they experience without knowing what intervention they have received, which helps to help avoid bias, and enables appropriate comparisons between the different interventions.

The starting dose of Resiquimod in the initial dose group will use a significantly lower dose than that used for nasal administration and therefore minimal if any symptoms are expected to occur. Up to three further groups will then be tested until an optimal dose is achieved which is able to generate an appropriate inflammatory response whilst being clinically tolerable for participants. A study flowchart with this information is outlined in the **Supplement**.

Why am I being asked to take part in this study?

You have been invited for this study because you are either a healthy volunteer or you have a diagnosis of asthma.

Where will this research project take place?

This project is being undertaken at Cambridge University Hospital Foundation Trust (CUHFT). The Screening visit and overnight stay will occur within the Cambridge Clinical Research Facility (CRF) https://www.cambridgecrf.nihr.ac.uk/ based within Addenbrooke's Hospital.

What will I need to do if I take part and how long will it take?

The first stage of the project is to undergo a pre-screening step to determine initial eligibility. This will be using a simple online screening tool, which will be available on our study website www.lungchallenge.org.uk. If eligible, we will be in touch by email or phone to invite you for a screening visit at the CRF.

At the screening visit we will undertake a medical assessment which includes asking you questions about your medical history, performing a brief medical examination, and undertaking routine baseline assessments, after which we will be able to determine your eligibility for the study.

If you are eligible for enrolment into the study, you will spend **1 week** in the study. The approximate **duration** of time it will take for each of your visits is outlined below:

Screening Visit: Up to **3 hours**

Visit 1: Anytime up to 2 weeks after screening for about **24 hours** including an overnight stay

Visit 2: 48 hours after the challenge for about **1 hour**

Visit 3: 7 days after the challenge for about **1 hour**

What happens at the screening visit?

The screening visit is to ensure you are suitable for the trial and will involve the following:

- **Medical history**: You will be asked about any medication you are taking and details of your allergies and other relevant medical history. Personal details will be taken. If you have asthma, you will also be asked to complete an asthma control questionnaire (ACQ).
- **Physical examination:** The study doctor will perform a general physical examination including examination of your heart and lungs.
- **Observation of vital signs and assessment of airway flow:** Your blood pressure, pulse, temperature, oxygen levels and breathing (using spirometry) will be measured.
- **ECG:** An electrocardiogram will be performed to get a tracing of your heart activity. This test is a routine procedure commonly done for clinical trials and is painless.
- **Blood tests:** Approximately 31.5 ml of blood (about 2 tablespoons) will be taken for routine safety tests, DNA analysis and cell isolation.
- **Urine tests:** A pregnancy test will be performed for all females. This is a routine part of most clinical trials.

- **Skin prick test:** Skin prick testing will be performed to establish if you are sensitive to grass pollen and other aeroallergens. This is because people's immune responses can vary depending on whether they have allergies. This involves placing a drop of allergen extract on the surface of your forearm, through which we press a sterile lancet into the surface of your skin. This is not painful and does not draw blood. With a positive reaction within a few minutes, the skin can become slightly itchy with a wheal (lump). This should go away within an hour. Antihistamines should not be taken in the 48 hours prior to screening.

- **Nasal sampling:** A nasal swab may be taken for SARS-CoV-2 testing if required by local or national policies at the time of sampling. A nasal brush will also be gently rotated in the inside of your nose for a few seconds to collect cells from the inside of your nose. Samples have been taken from many adults and children before with little or no discomfort. This may make your eyes water slightly. It may also cause some minor bleeding, but this is rare. The cells will then be sent for analysis or cultured for further study in the research laboratory.

- **Induced sputum**: In order to collect sputum from your lungs, a small amount of salty water (hypertonic saline) will be nebulised as a fine mist into your lungs over a few minutes and you will asked to cough at regular intervals in order to collect sputum. This is a safe and very well tolerated procedure. We will also administer a commonly used drug called salbutamol (the same drug used in asthma inhalers) to help open your airways. The whole procedure can take between 20 – 60 minutes depending on the volume of sputum produced. If you have asthma, this test will be done approximately 7 days after asthma diagnosis testing (see below).

- **Asthma diagnosis testing:** For volunteers with asthma, we will need to help confirm their diagnosis with an objective test. Depending on what their baseline airway function is, this test may be done in different ways (and will be decided at the screening visit):

    - **Reversibility testing:** They could be asked to perform breathing tests before and after inhalation with salbutamol to see if there is an improvement in airway function

    - **Methacholine challenge:** This is a test of airway responsiveness. The test looks at how "twitchy" your airways are by seeing whether they narrow after breathing in a substance called methacholine. You may not experience any symptoms, or you may have some chest tightness, wheeze, cough or shortness of breath. If the test shows tightening of the airways, you will be given salbutamol to open-up the airways. The effect of the methacholine is easily reversible once the test is complete. You should avoid taking your inhalers on the morning of the test.

    - **Alternative challenge test:** Depending on access and availability of other tests at Addenbrooke's Hospital, a different challenge test may be used to test for airway responsiveness according to local policy, for example by using an exercise bike.

    - Further information on these tests is available on the Cambridge website: https://www.cuh.nhs.uk/our-services/lung-function-unit/bronchial-provocation-test/

What will happen during the study visits?

If you are deemed eligible after the screening visit, you will be enrolled into the study and undertake the first visit within the following 3 weeks.

Visit 1 (Day 1)

You will be invited to attend Cambridge CRF at about **08:00** and stay with us until approximately 09:00 until the following morning. The overnight visit will be in an en-suite room with provision of all meals and refreshments, and regular monitoring by healthcare staff throughout your stay.

You will be randomised to receive nebulisation with either Resiquimod or Saline.

The following procedures will be performed as part of the visit:

- **Measurement of vital signs:** Your pulse, blood pressure, oxygen levels and temperature will be measured regularly every few hours throughout your visit.
- **Spirometry:** You will be asked to blow out into a small machine called a spirometer to assess airway function regularly every few hours throughout your visit.
- **Nasosorption:** We will use a small strip of absorbent material to soak up moisture from the inside of the nostril for a duration of 1 minute, taken once before and 24 hours after challenge to measure immune responses in the nose. This is a non-invasive and painless test but can cause a slight tickling sensation and may cause your eyes to water a little.
- **Blood**: Blood will be collected on 6 occasions: prior to challenge and up to 24 hours later.

Visit 2 (Day 2)

This will occur 48 hours after the initial inhaled challenge and will last for about 1 hour. It will involve assessment of vital signs, airway function, reporting of symptoms and blood tests.

Visit 3 (Day 8)

A final visit will take place 7 days after the initial inhaled challenge and will last for about 1 hour. It will involve assessment of vital signs, airway function, reporting of symptoms and blood tests.

The total volume of blood collected during visits 1-3 will be about 66 mL (about 3½ tablespoons).

Visit 3 will be the end of the study visit for you.

What can I do during the study visit?

You will be allocated your own room with an en-suite bathroom for the duration of your visits. There will be intermittent assessments and procedures performed in the daytime, but you will be left undisturbed at night-time unless you need medical or nursing attention.

You are encouraged to bring along your own entertainment such as laptops, tablets, and books. You will have access to Wi-Fi during your stay.

What are the possible benefits of taking part?

There are no specific benefits to you directly, but the results and findings from the research study may help discover new treatments that help other people in the future.

What are the disadvantages/risks?

Nasal spray with Resiquimod is well-tolerated when given as a nasal spray and there have been no reports of serious side effects. It is designed to mimic a mild viral infection and can therefore cause minor symptoms in some people. The previous trial of nasal Resiquimod resulted in the following mild symptoms: nasal blockage (30% of participants), lethargy (17%), headache (9%), muscle ache (3%) and sore throat (3%). Typically these symptoms lasted for a few hours and were gone by 24 to 36 hours.

The present study aims to nebulise a small volume (1 mL) of Resiquimod into the lungs with a similar aim to cause short-lived inflammation that mimics a mild viral infection. Similar symptoms to nasal challenge with Resiquimod are anticipated but in addition participants may also experience a mild cough. If volunteers experience a high fever associated with symptoms – paracetamol will be offered. The research team will regularly monitor all participants. This will include measuring spirometry particularly in volunteers with asthma. If there is a significant decline in airway function (> 20%), salbutamol will be given to help open-up the airways.

There are minimal if any side effects anticipated from the induced sputum procedure and salbutamol will be given to open-up the airways at the same time of administration in healthy and asthma participants, but recognised side effects of the procedure include cough and a tight chest.

As with administration of any drug or medicine, there is an extremely small risk of an anaphylaxis type reaction (a severe, life-threatening allergic reaction). You will be continuously monitored during procedures and emergency provisions are in place should you have a reaction. There is effective treatment for anaphylaxis kept on site and you will be treated promptly.

There is a very rare and unlikely possibility of a serious generalised response to Resiquimod. You will be continuously monitored during procedures and emergency provisions are in place should this occur.

It is possible, but very unlikely that you will have a reaction to the sampling procedures we are carrying out. The nasal sampling procedures may cause minor discomfort including watering of the eyes and a very minor degree of bleeding, which will likely be self-limiting. Taking a blood sample may cause mild to moderate pain and may result in temporary bruising to your arm.

How quickly can I resume my daily activities?

You will be directly monitored for the first 24 hours after nebulised challenge within our clinical research facility and anticipate that if you do experience any symptoms, then the majority of these will have resolved within this time. After this point you are free to return to your normal activities including work. However, we recommend that you avoid major exertional activities (e.g. going to the gym) until you feel completely well or after your final visit on day 7 after the inhaled challenge.

Will I be reimbursed for taking part?

We do not specifically pay people for taking part in this study. However, you will be reimbursed for the time you contribute to the study. Participants will be paid **£200** if they are enrolled into the study (meaning if they are eligible after the screening visit). Reasonable travel costs using economic means (e.g. public transport) to attend Addenbrooke's Hospital will also be reimbursed. Meals and snacks will be provided for their overnight stay within the research facility. If you are able to inform us in advance, we will do our best to accommodate any specific dietary needs.

What happens to the samples taken from me?

The samples collected during the study will be used to look at how the lungs and blood respond to Resiquimod. We will characterise the different cell types in your samples, look at gene activity and measure inflammation by looking at protein levels in sputum and blood. We will also collect and grow cells for culture in a laboratory and then freeze them down for future use. These expanded cells will be stored in appropriate conditions within the University of Cambridge. **All samples will be anonymised**. After the end of the study, samples will be stored for future analysis according to the recommendations in the Human Tissue Act and in a laboratory licensed by the Human Tissue Authority on the University of Cambridge site for up to 5 years and will then be destroyed.

We may also collaborate with external colleagues such as those in the pharmaceutical industry to utilise their expertise in analysing complex datasets, to help better understand immune responses, and try and identify molecules and targets to develop new therapies.

We consider your donated samples as a "gift", which means it is given as a donation without receiving specific payment for the sample and without conditions. It is a non-returnable gift. In case an invention results from the research undertaken with your sample, you will not receive any compensation for those discoveries. We will work in partnership with industry to successfully develop any invention for the benefit of patients.

Will any genetic tests be done?

Genes are made out of DNA, which forms the code for the production of proteins inside cells. Variations in genes between individuals may lead to variation in the proteins being produced.

We will also use blood samples to study your genetic make-up to understand why people respond differently to Resiquimod. This is not the sort of analysis that would give information about any other diseases or genetic conditions you may have and as such the results will not be available to you.

Anonymised data containing genetic information will be placed on publicly accessible databases to share and archive the data for the benefit of the wider scientific community. For example, data may be placed with The European Genome-phenome Archive (EGA) (https://ega-archive.org/) or/and the Human Cell Atlas (https://www.humancellatlas.org/).

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.

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.

Will my General Practitioner/family doctor (GP) be informed of my participation?

Given that you will only be involved in the study for one week and be closely monitored by the research study team, including direct observation for the first 24 hours, we will not routinely inform your GP of your enrolment into the study. However, we would be happy to do so if this is required.

Thank you for reading this information and for considering taking part in this research.

Please feel free to ask the study team any further questions that you may have.

Supplementary Information

What will happen to the results of the research study?

Results will be presented at conferences and published as scientific papers, but you will not be identified in any report or publication. The results will not impact your clinical care. In collaboration with academic and industry colleagues we hope to compare the cells from different patients and test and develop novel approaches to treating lung disease.

Who is organising and funding the research?

The project is organised by lung and immunology doctors and researchers at the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust. The project is funded by the Medical Research Council (MRC), part of United Kingdom Research and Innovation (UKRI) https://www.ukri.org/councils/mrc/.

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

You can find out more about how your information will be used at: www.hra.nhs.uk/information-about-patients, or by asking one of the research team, and contact details are provided at the end of this document.

Who has reviewed the study?

All research in the NHS is reviewed by an independent group, called a Research Ethics Committee, who check that the study will protect your safety, rights, well-being, and dignity. The project has also been approved by a committee of doctors and scientists at the University of Cambridge

You will be given a copy of the information sheet and a signed consent form to keep.

How will we use information about you?

We will need to use information from you, from your medical records and may also need to get information from your GP for this research project.

This information will include your initials, NHS number, name, and contact details. We 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.

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.

You can find out more about how the Sponsors use your information using the information below:

- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: cuh.gdpr@nhs.net.

- For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance/, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk

Participation in future research

We will ask if we can contact you about future studies. This is optional: you can take part in the current study and decline to be contacted again. Agreeing to be contacted does not oblige you to take part in any future research. You can also withdraw your consent to future contact.

What would happen if I have given informed consent but then lose the capacity to consent during the study?

You would be withdrawn from the study. Any identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to you.

What happens if something goes wrong?

If you wish to complain about any aspect of the way you have been approached or treated, the normal National Health Service complaints mechanisms will be available to you at Cambridge University NHS Foundation Trust.

If you have any concerns about your experience due to your participation in the research, please contact the local Patient Advice and Liaison Service (PALS) by phone on 01223 216756 or email cuh.pals@nhs.net. The PALS service can also be used to ask for more advice about taking part in research.

University of Cambridge holds insurance policies which apply to this study. If you can demonstrate that you experienced serious and enduring harm as a result of your participation in this study, you may be eligible to claim compensation without having to prove that University of Cambridge is at fault. If the injury resulted from any procedure which is not part of the study, University of Cambridge will not be required to compensate you in this way. Your legal rights to claim compensation for injury where you can prove negligence are not affected. Please contact the Principal Investigator if you would like further information about the insurance arrangements which apply to the trial.

Study Team Contact

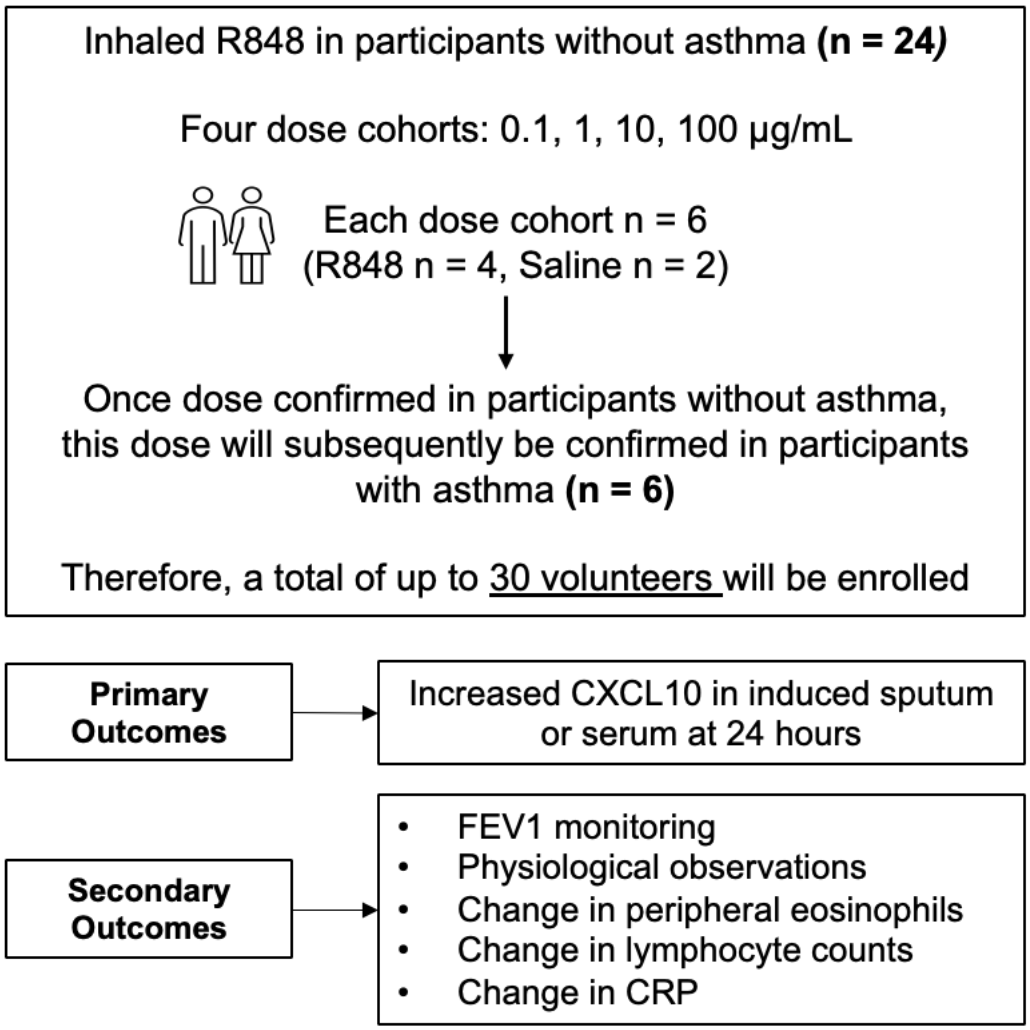
Dr Akhilesh Jha, Clinician Scientist and Honorary Consultant in Respiratory Medicine
Victor Phillip Dahdaleh Heart and Lung Research Institute,
University of Cambridge, Cambridge Biomedical Campus,
Hills Road, Cambridge. CB2 0BB

Contact via Addenbrookes Hospital switchboard on 01223 245151 or via CCRC on 01223 254800.

SUPPLEMENTARY APPENDIX A: STUDY FLOWCHART

Lung Immune Challenge Study:

Controlled Exposure to Inhaled Resiquimod (R848) to Study Mechanisms of Inflammation



SUPPLEMENTARY APPENDIX B: SCHEDULE OF PROCEDURES

Procedure	Screening Healthy (n = 24)	Screening Asthma (n = 6)	Day 1							Day 2	Day 8
			Visit 1							Visit 2	Visit 3
			0h	Challenge	15 min	1 h	4 h	8 h	24 h	48 h	Day 7
Informed consent	X	X									
Demographics, Medical History, Medications	X	X									
General physical examination	X	X									
ECG and baseline laboratory tests	X	X									
DNA blood test + PBMC isolation	X	X									
Nasal brush	X	X									
Skin prick testing for aeroallergens	X	X									
Bronchodilator reversibility, methacholine challenge or test as per CUH policy		X									
Induced sputum	X	**7 Days Post Reversibility**							X		
Nasosorption			X						X		
Spirometry (FEV_1) and Observations (temperature, pulse, blood pressure)	X	X	X		X	X	X	X	X	X	X
Serum			X		X	X	X	X	X	X	X
Full blood count + C-Reactive Protein			X				X		X	X	X
Nebulisation with R848 or Saline				X							