



PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

Keratinocyte Growth Factor - promoting thymic reconstitution and preventing autoimmunity after alemtuzumab (Campath-1H) treatment of multiple sclerosis

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this study and what will happen to you if you take part.

Section 2 gives you more detailed information about the conduct of the study.

Section 1: Purpose of the study and what will happen

1. What is the purpose of the study?

The purpose of this study is to try and prevent side effects of alemtuzumab - a drug which has been tested in clinical trials as a treatment of multiple sclerosis.

In multiple sclerosis (MS) the patients' own immune system attacks their brain and spinal cord causing damage. Alemtuzumab could be the most effective drug treatment of multiple sclerosis tested to date; not only does it prevent new attacks, it also may prevent disability. Alemtuzumab works by binding to and killing immune cells (lymphocytes) which normally fight infections but which mistakenly attack nerves in multiple sclerosis. Following treatment the immune system grows back, but without the immune cells which cause multiple sclerosis. Although effective, alemtuzumab has side effects, in particular 1 in 3 patients develop a new autoimmune disease after treatment. In other words, as their immune system grows back, it begins to attack other parts of their body; most commonly the thyroid gland.

We believe that we can reduce the risk of autoimmune disease after treatment with alemtuzumab by using a drug which alters the way in which the immune system grows back. Kepivance (also known as Palifermin) has been shown to do this in animals. It works by boosting the function of the thymus, a gland in the neck which makes new immune cells. This study is testing whether or not Kepivance will boost thymus function in humans.

2. Why have I been invited?

You have been invited to participate in this study because you have active relapsing remitting multiple sclerosis and we believe that you would benefit from treatment with alemtuzumab. We plan to include 80 patients with multiple sclerosis from across the UK. All patients will be treated at the Clinical Research Facility (CRF), at Addenbrooke's hospital in Cambridge.

3. Do I have to take part?

Participating in this study is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time without giving a reason. If you chose not to participate or to leave the study, your future medical treatment and normal standard of care will not be affected in any way.

4. What will happen to me if I take part?

If you agree to participate in the study, you will be asked to sign the Informed Consent Form at the end of this document. You will be given a copy of this to take away and refer to later.



4.1 Screening visit

After signing the informed consent form, you will be given an appointment for a screening visit. During this visit a study doctor will run through a checklist to make sure that you are suitable to take part in the study. This visit will take around 40 minutes. Your MS history and medications will be reviewed and recorded and the doctor will perform a physical and neurological examination. Blood will also be taken at this visit (approximately 100mls or about 6 tablespoons) for a number of laboratory tests. A urine sample will also be taken (for women of childbearing potential a pregnancy test will also be done).

It will take a few weeks for these test results to come back. Once we know that you are suitable for the study, we will contact you, by telephone, to confirm this. If you are taking beta interferon or copaxone, you will be asked to stop taking them as you must be off these treatments for at least 1 month before starting alemtuzumab. At this stage we will randomly assign you to receive either kepivance or placebo. **All patients will be treated with alemtuzumab.**

4.2 Randomisation

Because we don't know for certain that Kepivance will prevent autoimmunity after alemtuzumab treatment, half of all patients in this study will be assigned to receive Kepivance and the other half will be assigned to receive a "dummy drug", called a placebo. It looks the same as the Kepivance treatment but does not contain any of the active ingredients and will have no effect on you. This process will be done in a random way (by chance) - much like flipping a coin. You will have a 50% chance of receiving Kepivance.

All patients will be treated with alemtuzumab.

This study is "double-blinded", meaning that neither you nor your study doctor will know which treatment you have been assigned to, although it is possible for your study doctor to find out if necessary.

4.3 Baseline assessments and treatment

Chest CT scan

You will be asked to attend Addenbrooke's hospital for a CT (computed tomography) scan of your chest to look at your thymus gland. Your thymus sits in your chest, lying in front of your heart and behind your breastbone (sternum). You will have a repeat CT chest scan six months following treatment with alemtuzumab.

Starting treatment

You will be asked to attend the Clinical Research Facility (CRF) at Addenbrooke's hospital to begin your treatment. When you arrive, you will be seen by a study doctor who will check that you are well, free from infection and (for women of childbearing potential) that you are not pregnant. If you and the study doctor are happy, you will receive your first dose of Kepivance or Placebo. This will be given by injection into a vein in your arm. You will have two further doses over the next two days. Although each injection takes only a few minutes, you will be observed by medical staff for at least an hour after each dose to make sure that you are well and do not experience any side effects.

After a two day break, you will be admitted to hospital to start treatment with alemtuzumab. Alemtuzumab is given by a drip or "infusion", into a vein in your arm. You will receive 5 infusions over 5 consecutive days. Each infusion takes about 4 hours. On days 1 to 3, you will be given a steroid called methylprednisolone, into the same drip, prior to starting alemtuzumab. Each dose of methylprednisolone takes about an hour. Methylprednisolone is given to reduce the side effects of the alemtuzumab infusion.

It is routine practice for people to go home between alemtuzumab infusions. However, if you are



feeling unwell or if the study doctor feels it would be in your best interest, you may be asked to stay in hospital overnight. Following your 5th infusion, you will be given a two day break, before being asked to attend hospital for 3 further injections of Kepivance or placebo.

4.4 Follow up visits and ongoing treatment

You will be seen by a study doctor one month after starting treatment, then every three months for the rest of the study. At each visit a study doctor will assess how well you have been; they will ask about your MS, if you have had any side effects from your treatment, and they will review your regular medications. You will also be asked to give a blood sample (about 100mLs, or 6 tablespoons full) and to provide a urine sample.

You will be retreated with alemtuzumab and Kepivance/placebo at month 12. The only difference being that alemtuzumab will be given over three days instead of five.

At months 1, 3, 13 and 15 (that is one and three months after each round of alemtuzumab) you will be asked to attend the CRF as a day case to receive "top up doses" of Kepivance or placebo. Each top up dose will be 3 injections given over 3 consecutive days.

4.5 Monthly FBCs

You will need a monthly full blood count following treatment (except in the months you have to attend clinic for the study assessments). This is a simple blood test, which can be done at Addenbrooke's Hospital. If it is more convenient for the test to be done at your local GP practice, and if your GP agrees, then we can arrange that. In which case, we will also arrange for us to receive the results of the test: either directly from the laboratory, or from your GP practice. In all situations, we will undertake the responsibility for checking that the blood test has been done and acting on the results.

4.6 Duration of the Study

Your involvement in the study will last 30 months from starting treatment. At the end of the study you will be asked to enroll in a long term safety monitoring study (where patients are seen twice a year on average). Enrollment in this follow up study is entirely voluntary and details and will be provided to you nearer the time (month 28 onwards).

Please refer to the schedule of events (over page) for a summary of what is involved in taking part in this study.



Schedule of events summary

	Screening	Baseline	Days - 5 to -3	Day 1 to 5	Day 8-10	Month 1	Month 3	Month 6	Month 9	Month 12: days -5 to -3	Month 12: day 1-3	Month 12: day 8-10	Month 13	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	
Sign consent form	x																			
Consultation with doctor	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
General examination by doctor			x	x	x	x														
Neurological examination	x							x							x					x
Blood tests at Addenbrooke's	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Monthly blood tests	<i>Monthly blood tests done either at GP surgery or local hospital or Addenbrooke's Hospital</i>																			
Urine test	x	x	x			x	x	x	x	x			x	x	x	x	x	x	x	x
Chest CT scan		x						x												
Treatments																				
Palifermin or Placebo drip			x		x	x	x			x		x	x							
Alentuzumab drip				x							x									
3 days steroid drip				x																
1 month of oral Acyclovir				x																



5. What will I have to do?

We know taking part in a study can be quite daunting, so if you decide to take part we will guide you through what is required from you.

- If you are already on medication for your multiple sclerosis (for example beta-interferon or copaxone) you will be asked to stop it before being treated with alemtuzumab. You will remain off this medication for the duration of the study. We will tell you when to stop your medication, it is important that you do not stop your treatment until we tell you to.
- It is important that you take any study medication we give you regularly and as directed. You will also need to keep an accurate record of any other medication you take during the course of the study, and to let the study team know at each visit. You should not take any herbal medicines as we do not know how these may react with the study drug. If you are unsure whether you can take any over-the-counter or prescription medications whilst in this study, please contact a member of the study team for advice.
- Do not have any vaccinations during the course of the study without discussing them with the study doctor beforehand. Most vaccinations are safe to have, but live or attenuated (weakened) vaccines are not permitted.
- Study medicines may harm an unborn baby or nursing infant. You will not be able to take part in this study if you are pregnant or breastfeeding. You should not participate if you are planning to become pregnant or father a child during the study. Women of childbearing potential must use one of the following, reliable forms of contraception for the entire duration of the study. These include:
 - Oral contraceptives (either combined or progestogen alone)
 - Contraceptive implants, injections or patches
 - Vaginal ring
 - Intrauterine device (IUD, coil or intrauterine system)
 - Condom **and** cap or diaphragm **plus** spermicide (chemical that kills sperm)
- Men must use a condom and spermicide (chemical that kills sperm), even if female partner(s) is using another method of contraception for the duration of the study. If you or your partner becomes pregnant during the study you should inform your study doctor immediately. Your study doctor will discuss all the options available to you. The outcome and progress of any pregnancy would be followed and you would be asked questions about the pregnancy and baby, if appropriate.
- You should tell the study team if you feel unwell or different in any way during the study. If you have any major concerns or are feeling very unwell please contact your study doctor immediately using the contact numbers at the end of this information sheet.
- You should discuss your participation in this study with any private medical, protection or life insurance provider you use, as failure to notify them may affect or invalidate your cover.

6. What is the drug being tested and what are the side effects?

Kepivance is the trade name for a drug called Palifermin. It is an artificial form of a growth factor already present in your body. This growth factor is called keratinocyte growth factor, or KGF. Like KGF, Kepivance has been shown to protect the cells that line our mouths and cells in the thymus.

Because of its protective affect on the tissue that lines the mouth, Kepivance is already in regular



clinical use to reduce the duration and severity of mouth ulcers in adult patients receiving chemotherapy and radiotherapy. In these patients Kepivance is well tolerated. To date, no long term or life-threatening side effects have been reported in these patients.

Mouth symptoms.

The most commonly reported adverse effects of Kepivance (reported in > 1/10 patients) is the feeling of increased thickness of the tongue and gums. This may be associated with an alteration in taste. Both these side-effects usually occur approximately 6 days following 3 consecutive daily doses of Kepivance, and last roughly 5 days. Less common symptoms (occurring between 1/10 and 1/20 patients) are: an alteration of taste, a white film coating on the tongue and impaired taste. These all resolve within days.

General Side-effects

Other side-effects seen in clinical trials more commonly after Kepivance than placebo are:

- **Skin rash** in 55% of Kepivance patients versus 46% with placebo
- **Skin redness** in 44% of Kepivance patients versus 30% with placebo (from our experience of giving Kepivance, skin redness and skin heat is a very common side-effect. The redness can be marked, but is typically short-lived (lasting a few days only).
- **Skin itching** in 50% of Kepivance patients versus 30% with placebo
- **Cough** in 32% of Kepivance patients versus 26% with placebo
- **Numbness** (generally of 1 body area, including the feet, fingers, and around the mouth) in 10% of Kepivance patients versus 4% with placebo

In addition, on this trial, a minority of patients receiving treatment with Kepivance have described increased scalp hair shedding leading to "thinning" of their hair. In most cases this has been mild; but in a small number of patients hair loss has been more noticeable. In all cases this side-effect has resolved within a few weeks to a few months after treatment; and all patients have said that their hair has returned to normal. This side effect has not been reported in other studies of Kepivance.

We will be giving higher doses than is usually used in routine clinical practice. We have selected the dose by performing a dose-tolerance study. We have chosen the highest dose tested shown to be tolerated by patients with multiple sclerosis receiving treatment with alemtuzumab, which is 180mcg/kg/day.

7. What are the possible disadvantages and risks of taking part?

Attending hospital and blood tests

If you decide to take part in this study you will be required to attend Addenbrooke's hospital for treatment and for regular follow up visits. You will have monthly blood tests (most of which can be done at your local GP surgery). These may cause mild discomfort and bruising of the skin.

Risks of CT scanning

During the course of the study you will have two CT (computed tomography) scans of your chest; one at baseline, the other six months after treatment. CT scans are carried out by using a special X-ray machine, which produces an image of a cross-section, or slice, of your body. The scanner consists of a 'doughnut-shaped' structure, or gantry, about two feet thick with a hole in its centre, through which you pass while lying on a couch. A narrow fan-shaped beam of X-rays is produced from inside the gantry and rotates in a complete circle around you. The X-rays pass through your



body and are detected by electronic sensors on the other side of the gantry. This information passes to a computer which produces a picture of the internal structure of the body. The pictures are displayed on a screen for examination by the radiologist.

You will not be required to have any special preparation or injections prior to the scan. You will not feel any pain although occasionally you may feel a slight discomfort arising from having to lie flat for 5 minutes, although the actual scan takes only approximately 5 seconds. CT scanning involves the use of X-rays. Women who are or might be pregnant must inform a member of staff in advance, as the fetus is more sensitive to radiation. The amount of radiation used is more than an ordinary X-ray of the chest or body and is equal to the natural radiation that we receive from the atmosphere over a period of approximately one year.

Risks associated with medication

Half of all patients on this study will be given Kepivance - the side effects of which are described in section 6. All patients will be treated with methylprednisolone, alemtuzumab and acyclovir. These drugs also have potential side effects as outlined below:

a) Methylprednisolone

Methylprednisolone can cause facial flushing and insomnia in some patients. These side effects resolve once the treatment is stopped. In some people methylprednisolone can alter their mood, making them either depressed or agitated. Methylprednisolone can also irritate the lining of the stomach and medications may need to be given to counteract this. Very rarely high dose methylprednisolone can cause severe damage to the bones (most often the hip) requiring surgical joint replacement.

b) Alemtuzumab

Infusion- related side effects

Almost all patients who receive an infusion of alemtuzumab experience at least some side effects during or shortly after the infusion. You will be given medications to help reduce or eliminate these symptoms. These symptoms most commonly include:

- Rash (raised itchy red spots on the skin) and/or itching that respond to antihistamine medication
- Fever, headache, and fatigue – may last for a few hours
- Nausea, vomiting, diarrhea, or a bad taste in the mouth
- Worsening of current or old MS symptoms. This usually lasts only for a few hours and does not lead to permanently increased disability
- Shaking and chills
- Difficulty sleeping
- Chest discomfort
- Shortness of breath and/or spasms in the windpipe, especially in patients with asthma
- A drop in blood pressure that may cause dizziness
- Rapid or slowed heartbeat

These infusion-associated side effects can sometimes be serious and life-threatening. In patients treated with alemtuzumab for MS, these serious disorders include chest discomfort, shortness of breath and abnormal heartbeat. Infusion-associated side effects have also occurred in patients treated with alemtuzumab for conditions other than MS, when patients received higher total dose of alemtuzumab. In these patients, the serious disorders included allergic (anaphylactic) reactions and severe lung or breathing disorders that required breathing machines to be used.

New Autoimmune disorders

From previous studies, we know that about 1 in 3 patients with MS treated with alemtuzumab develop a new autoimmune disease. That is, as their immune system recovers from treatment, it produces antibodies (a type of protein), that bind to and damage another part of their body. These types of antibodies are called auto-antibodies. In the vast majority of cases, auto-antibodies after



alemtuzumab bind to and damage the patients' thyroid gland (uncommonly they bind to and damage blood platelets, and very rarely they can bind to and damage the patients kidneys). A further 1 in 3 patients develop harmless auto-antibodies after alemtuzumab. These antibodies can be measured in the blood, but even if they are present they cause no damage.

We hope those randomized to receive Palifermin will have a reduced risk of developing both harmful and harmless autoantibodies after alemtuzumab - this idea is what this study is designed to test.

(1) Thyroid problems

The thyroid can become overactive or underactive.

- Signs of an overactive thyroid include: sweating, weight loss, eye swelling, nervousness or heart palpitations.
- Signs of an underactive thyroid include: weight gain, feeling cold, fatigue and constipation.

An infrequent symptom associated with an overactive thyroid is swelling around the eyes, which can be very difficult to treat. This symptom is more common if you smoke.

Thyroid disease is generally easily treated but some patients will need to be treated for life. Less common is an underactive thyroid after treatment with alemtuzumab. The symptoms are easily treated by taking thyroid hormone replacement tablets; usually required lifelong.

Your thyroid function will be monitored carefully throughout the study. Usually we detect changes in thyroid function before symptoms develop.

(2) Low Platelet Count (Immune Thrombocytopenic Purpura, or ITP)

In a previous study of alemtuzumab in MS patients, approximately 3% (3 out of 100) of MS patients who received alemtuzumab experienced a sudden, severe decrease in a kind of blood cell which helps your blood clot, called platelets. The main complication of a low platelet count is bleeding, which could be fatal. During this study, if you experience any disorder that could cause uncontrolled bleeding, for example, a bleeding stomach ulcer or severe high blood pressure, you may be at increased risk of suffering these more serious consequences from low platelet levels. A low platelet count can cause you to experience any of the following symptoms:

- Easy bruising
- Easy bleeding of the gums
- Nosebleeds
- Unusually heavy menstrual periods
- Any other unusual bruising or bleeding

Your platelet count will be monitored on a monthly basis throughout the course of study (a simple monthly blood test). We will let you know if your platelet count drops and provide further information if appropriate. **If you develop signs or symptoms such as easy bruising, gum bleeding, nosebleeds, heavy periods, or any other bleeding you must contact your study doctor immediately.** Treatment for ITP includes steroids and intravenous infusions of antibodies ("IVIG"). (Please note that an operation called splenectomy, and a drug called romiplostim, are sometimes used to treat "ordinary ITP", but to date have never had to be used for ITP due to alemtuzumab).

(3) Kidney disease

Less than 1% of patients who received alemtuzumab have developed a disorder of the kidneys. Goodpasture's disease (also known as anti-glomerular basement membrane or anti-GBM disease) can result in severe damage to the kidneys and possibly lead to kidney failure or the need for dialysis and/or kidney transplantation. Less commonly, this disease can cause bleeding of the lungs, or death although this has not happened in MS patients treated with alemtuzumab. Patients may not have any warning symptoms of this disease but may experience:

- Blood in the urine
- Coughing up blood



- Swelling, especially in the legs and feet

Infection

Alemtuzumab treatment always causes an immediate reduction in the white blood cells called lymphocytes, and this reduction can last for several years. Patients who receive alemtuzumab are at an increased risk of infections, particularly in the first few months following treatment. If severe, these might require hospital treatment and have the potential to lead to death, although fatal infections have rarely occurred in MS patients treated with alemtuzumab. Most fatal infections have been reported in patients with diseases other than MS who received alemtuzumab therapy at different doses. Most of these patients were particularly vulnerable because they had cancer, had received multiple chemotherapy treatments, and were elderly.

Your risk of infection may be higher if you receive another immune suppressing drug either before or after alemtuzumab. At a minimum, you should avoid treatment with drugs that can reduce the function of your immune system for a period of at least 1 year after alemtuzumab treatment. Some MS treatments should not be administered to patients who have recently received alemtuzumab so participation in this study may limit your choice of subsequent MS therapies.

To lessen your chance of developing certain types of infections or lessen the severity of an infection, you will be asked to comply with the following recommendations:

- Herpes Simplex Type 1 and 2: An anti-viral medication (acyclovir or similar medicine) designed to prevent herpes will be given to all alemtuzumab patients starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day of the cycle.
- Varicella (chicken pox or shingles): If possible, you should avoid contact with anyone who has symptoms of chicken pox or shingles, especially within the first few weeks after alemtuzumab. If you are exposed, you should tell your study doctor as soon as possible, so that your level of immunity to varicella can be checked.
- Food-borne illness: For at least three months after each alemtuzumab dose, there is an increased risk of certain infections that are usually spread by foods. You should avoid raw or undercooked eggs, meats and fish; unpasteurized milk, cheese and blended fruit/vegetable drinks; and improperly refrigerated foods.
- Vaccines: To minimize the risk of infection after alemtuzumab, you should receive all vaccinations recommended by your public health authorities, except live vaccines. It is important that you check with your study doctor prior to receiving any vaccine during this study. It is also important that other members of your household are immunized according to recommended schedules, preferably before you enter the study. We do not recommend that you have any particular vaccinations prior to alemtuzumab.

Cancer

It is possible alemtuzumab might interfere with the body's ability to find and destroy cancer cells. There have been reports of cancer, which can be fatal, in patients who received alemtuzumab. For example, blood cells cancers (lymphoma) and tumors of the thyroid gland have been reported. There is currently not sufficient information to draw conclusions regarding the risk for cancer in alemtuzumab-treated MS patients.

Women with human papilloma virus (HPV) infections of the uterine cervix are at increased risk of developing cervical cancer. That risk may increase after treatments, such as alemtuzumab, which act on the immune system. We would therefore encourage women taking alemtuzumab to ensure that they have their routine smears as offered by the cervical smear screening service. Patients with a history of basal cell carcinoma should be followed closely by their dermatologist following alemtuzumab treatment.

Blood Transfusions



If you need to have a transfusion of blood products after you receive alemtuzumab, you need to tell your doctor that you should only receive irradiated blood products.

Fertility

From tests performed in female mice given alemtuzumab close to mating, it was shown that some become pregnant, but some mice released fewer eggs than usual from their ovaries, and fewer fertilized eggs were properly implanted in the womb. Therefore there is a possible risk that alemtuzumab may affect fertility in humans, but it is not yet known whether the dose that you are receiving in this study will pose a significant risk to you.

Risks to an Unborn Child

Alemtuzumab may be harmful to an unborn child. Animal studies in pregnant female mice given alemtuzumab found that most led to live births, but some mice lost their pregnancies. Baby mice exposed to alemtuzumab during pregnancy or breast feeding showed decreased numbers of lymphocytes, the immune cells that are targeted by alemtuzumab. Female patients of childbearing potential must have a negative urine pregnancy test prior to receiving any alemtuzumab treatment cycles. Both fertile male participants and female participants of childbearing potential in this study must agree to use an effective form of birth control (see section 5).

Some side effects of alemtuzumab may arise months or years after treatment, and could pose a risk to future pregnancies. In particular, infection and thyroid problems may put your unborn child at risk. You should discuss this with your study doctor or gynecologist/obstetrician, ideally before becoming pregnant, or at the earliest opportunity after pregnancy.

c) Acyclovir

To reduce the risk of you developing cold sores (caused by the herpes simplex virus) you will be asked to take acyclovir tablets for one month following treatment with alemtuzumab. Acyclovir is usually very well tolerated. The commonest side effects are nausea and diarrhea. It can rarely cause kidney problems. If you are intolerant of acyclovir for any reason your study doctor will prescribe an alternative for you.

8. What are the possible benefits of taking part?

There is no guarantee that you will benefit from taking part in this study. However, we do know that alemtuzumab treatment significantly reduces both relapses and disability compared to beta-interferon, and as such it should improve your MS and quality of life. Alemtuzumab has very recently been approved in the EU as a therapy for active relapsing remitting multiple sclerosis, but it is not yet routinely available on the NHS.

We do not know whether treatment with palifermin will reduce your risk of new autoimmune diseases after alemtuzumab treatment but the information collected as part of your participation in this study will provide us with the answer to this question and may benefit MS patients receiving alemtuzumab in the future.

9. What are the alternatives for treatment?

You do not have to participate in this study. Instead, you can discuss alternative treatments with your study doctor including approved medicines for multiple sclerosis such as beta-interferon, glatiramer acetate, or natalizumab. Alternatively, you may also decide not to receive therapy at this time.

10. What happens when the study stops?

At the end of this study you will be referred back to your local NHS neurologist for care of your multiple sclerosis.

We would invite you to enroll in a study called CAM-SAFE (A study of the long term safety and mechanism of action of alemtuzumab (Campath-1h) REC reference: 11/EE/0007). Patients on CAM-SAFE are seen at Addenbrooke's once or twice a year and monitored for long term side effects of previous alemtuzumab treatment. Further treatment with alemtuzumab is not part of CAM-SAFE.



Involvement in this follow up study is entirely voluntary and you would need to sign a new informed consent form. Further details of this study will be provided to you nearer the time (month 28 onwards).

11. Expenses & Payment?

You will not receive any payment for participating in this study. However we can reimburse any reasonable travel and parking costs incurred by your participation in this study. We will also reimburse reasonable overnight accommodation costs for those coming from a long distance. It is important that you keep all receipts and request a claim form at your hospital visit, if appropriate. Details of how and when payments will be made are available from the study team.

Section 2: Study Conduct

12. What if new information becomes available?

Sometimes during the course of a study, new information becomes available which might affect your decision to continue participating in this study. Your study doctor will contact you to discuss the new information and whether you wish to continue participating in the study. If you still wish to continue on the study, you will be asked to sign a new Informed Consent Form.

The study sponsor, the regulatory authority or the study doctor may decide to stop the study at any time. If that happens we will tell you why the study has been stopped and arrange for appropriate care and treatment for you.

13. What if I decide I no longer wish to participate in the study?

You are free to come off this study at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, no more tests will be performed and you will not receive further treatment on this study. Any information already provided

or results from tests already performed on you or your samples will continue to be used in the study, however no further information will be collected or tests performed. Any samples already provided for the study can be destroyed if you wish.

The study doctor may also choose to withdraw you from the study if they feel it is in your best interests or if you have been unable to comply with the requirements of the study. Reasons for study withdrawal could include:

- You have experienced a serious side effect
- You are unable to complete the visits, medication or study documentation as required
- You become pregnant or plan to become pregnant
- The study doctor feels you no longer appear to benefit from the treatment.

If you have experienced any serious side effects during the course of the study which require you to withdraw from the study, your study doctor will follow-up with you regarding your progress until the side effect has stabilised or resolved. If you withdraw for other reasons you will be strongly encouraged to continue all safety assessments.

14. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to your study doctor who will do their best to answer your questions.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Addenbrooke's Hospital or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to



make a claim for this.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Patient Advice and Liaison Service (PALS) at Addenbrooke's hospital on 01223 216 756 or pals@addenbrookes.nhs.uk.

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

All information collected about you as a result of your participation in the study will be kept strictly confidential. Your personal and medical information will be kept in a secured file and be treated in the strictest confidence. You may ask to see your personal information at any time and correct any errors if necessary. Once you have agreed to participate in this study you will be allocated a unique study number which will be used on all your study documentation. This number will be linked to your personal information; however you will only be identified by this unique number.

We will need to inform your GP of your participation in this study so that any medical decisions made by your GP account for the treatment you are receiving as part of this study.

Authorised staff, who work for or with the sponsor of the study, the hospital R&D Department or the Regulatory Agency responsible for drug research may require access to your personal information and/or medical records to verify the data for this study and ensure that it is being conducted in accordance with UK law. All information will be treated in the strictest confidence during the review process.

16. What will happen to my samples?

We will ask you to donate your samples to the University of Cambridge, Department of Clinical Neurosciences. Your donated samples will be treated as "gifts", which means that the department

will have control over what happens to the samples, how they are used and all rights to any "inventions" (such as drug treatments or tests) which might come out of research performed using your samples.

Most of the blood you donate will be analysed on the day it is taken, however, some samples will be frozen for future studies. All stored samples will be kept in an anonymous way - labeled with your unique study number. Your sample will only ever be used for research that is approved and deemed appropriate by a Research Ethics Committee.

Will any genetic tests be done?

We would like to look at your genetic code (scientists call this your DNA) to see if any of the changes we see in the laboratory are genetically determined. For example, we would like to know if a person's "genetic makeup" makes them more or less susceptible to developing autoimmunity (e.g. thyroid disease) after alemtuzumab. DNA can easily be extracted from your blood sample – you would not need to give an additional sample. We will only look at parts of your genetic code. The results we obtain will not affect you as an individual, nor will they affect your family. We will not feedback any of the results we obtain to you or to anyone else (including your GP). Any DNA that remains unused will be destroyed on or before 1 January 2060.

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

The results of the study will be anonymous and you will not be able to be identified from any of the data produced. When the results of this study are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. If you would like to obtain a copy of the published results please contact your study doctor directly who will be able to arrange this for you.

18. Who is organising (sponsoring) and funding the study?

The study is being sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study is being funded by the Medical Research Council (MRC) and the Moulton Charitable Trust.

19. Who has reviewed this study?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES London (Hampstead).

20. Further information and contact details

If you have any questions about this study please phone the dedicated answer phone on: **01223 216187**. We will respond within one working day.

We can also be contacted by email:

Joanne Jones (Chief Investigator)	jls53@medschl.cam.ac.uk
Alasdair Coles (Co-Investigator)	ajc1020@medschl.cam.ac.uk
Karen May (Research Nurse)	km480@medschl.cam.ac.uk

In the event of an emergency please call:

The Addenbrooke's contact centre on **01223 245151** and ask to be put through to a member of the "Campath team" (Drugs Trial Rota).

Thank you for taking the time to read this document, and for considering taking part in the study.



INFORMED CONSENT FORM

Keratinocyte Growth Factor - promoting thymic reconstitution and preventing autoimmunity after alemtuzumab (Campath-1H) treatment of multiple sclerosis

Principal Investigator: Dr Joanne Jones

Participant Number:

If you agree with each sentence below, please initial the box

Table with 3 columns: Number, Statement, and Initial box. Contains 8 rows of consent statements.

Name of patient

Signature

Date

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Name of person taking consent

Signature

Date

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