(to be printed on local hospital headed paper)

AZTEC

A phase II study of the use of Azacitidine for the treatment of patients with chronic graft-versus-host-disease

PATIENT INFORMATION SHEET

We would like to invite you to take part in an early phase non-commercial clinical trial (also called clinical study).

- Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve for you.
- Please take your time to read the following information carefully, and discuss it with others if you wish. Take your time to decide whether or not you wish to take part.
- Ask us if there is anything that is not clear, or if you would like more information.
- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the trial.
- You are under no obligation to take part in this trial.
- Thank you for reading this information sheet.

Important things that you need to know

- We are aiming to look at whether it is safe to give a drug called azacitidine to patients who have a condition called 'graft-versus-host-disease' (GvHD) after undergoing a stem cell transplant. We also want to see whether azacitidine helps to improve the symptoms of GvHD.
- Like all medicines, azacitidine has side effects. A list of possible side effects can be found on page 7.
- Participating in the trial will involve many visits to your hospital to receive treatment and to be monitored to check how you are responding to the medication.
- We will ask you to donate small amounts of blood and a sample of tissue from a routine biopsy for research purposes.

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If you have any questions about this study, please talk to your doctor at

<< insert name and contact telephone number of Principal Investigator >>

Information Sheet - Part 1

1 Purpose and Participation

What is the purpose of the trial?

The aim of this trial is to find out if it is safe to give a drug called azacitidine to patients that have developed a condition called chronic Graft *versus* Host Disease (cGvHD) following a stem cell transplant and have become dependent on, or been unsuccessful with previous steroid treatment. We also want to see whether azacitidine is an effective treatment option in patients with this condition.

There are currently no standard treatment options for the stage of your disease and patients may be treated with a variety of different treatments, one of which may be a clinical trial.

The way that patients with cGvHD have their disease measured, both initially and following treatment, varies both within the UK and outside of the UK. A recent collaboration between leaders in this disease across the world has suggested a standard way of measuring cGvHD. This study will use this new system and assess if it is feasible to perform. It may involve more assessments that what is standard at your local hospital. All of the assessments involved are explained within this information sheet.

Why have I been invited?

You have been given this Information Sheet because you have been diagnosed with cGvHD and your doctor thinks you may be suitable to receive treatment with azacitidine. There is no standard treatment for this condition in patients that have either become dependent on steroids, are unable to tolerate steroids or where steroids have not been effective.

Do I have to take part?

No, participation in this trial is entirely voluntary. It is up to you whether or not you decide to join the trial. We will describe the trial and go through this information sheet with you. This information sheet is yours to take away. If you decide to take part, we will then ask you to sign a consent form to confirm that you understand what is involved when taking part in this trial. If you do decide to take part, you are free to withdraw at any time, without giving a reason. This will not affect the quality of care you receive. If you decide not to take part your treatment and standard of care will not be affected in any way.

What will happen to me if I take part?

1. Consent and Screening

If you decide to take part in this trial, we will ask you to give your written informed consent to take part by signing a consent form. The trial requires the following tests to be performed to determine whether you are suitable for the study.

- Blood tests
- Heart trace (electrocardiogram (ECG))
- A medical examination by a doctor or nurse. This will include height, weight, examination of your skin and mouth and questions about your overall health such as if you are having any problems eating or if you have experienced any diarrhoea.

- Functional assessment. You will also be asked to walk for 2 minutes (in the hospital) as quickly as you can and the distance you walk will be recorded. You can stop for a rest if you need to.
- Lung function tests (further details on page 4).
- 3 short questionnaires for you to complete about the symptoms of your GvHD (further details on page 5).
- Pregnancy test; if you are a woman and capable of having children, a urine test will be done before starting treatment to make sure you are not pregnant. This is to make sure that it is safe for you to receive the treatment.
- Biopsy of area affected by G*v*HD if your doctor thinks this is necessary
- Sample of blood for research

Some of these tests may already form part of your standard care. You may be asked to attend on different days to complete these tests. Once you have completed all the tests, your doctor will be able to tell you if you are suitable to go ahead with the trial.

2. Treatment

If the screening process shows that you are suitable for the trial, you will be asked to start the study medication: you will receive treatment with a drug called azacitidine. This drug has been widely used in patients with blood disorders such as acute myeloid leukaemia (AML) and myelodysplasia (MDS), however there is limited information on how it may work in patients with cG*v*HD. Research in the laboratory and previous studies have suggested there may be a role for azacitidine in the treatment of cG*v*HD.

Azacitidine will be given to you either as an injection just under your skin (subcutaneous injection) or an intravenous infusion (i.e. into your vein). Your study doctor will decide which of these two options is the best way to provide your treatment and discuss this with you. Treatment with azacitidine will be given for up to 6 cycles (with each cycle being 28 days – 4 weeks). You will receive treatment with azacitidine for 5 consecutive days at the beginning of each cycle . This means coming to hospital to receive your treatment daily from Monday-Friday. When you come to hospital for your azacitidine treatment, it is expected your visit will last between 1-2 hours. If your doctor thinks it is best to provide azacitidine intravenously, you may receive treatment through a Hickman line or a peripherally inserted central catheter (PICC line). A Hickman line is a narrow tube that is put into a vein in your chest to allow medication to be given directly into the bloodstream. A PICC line is similar but it is put into a vein above the bend of your elbow. If your doctor thinks this is the best way to administer your treatment, they will discuss it with you in more detail.
If your doctor thinks you are benefiting from azacitidine treatment, you may receive up to an additional 4 cycles of treatment (up to 10 cycles in total).

3. Assessments

If you are able to take part in the trial, you will be assessed on the first day of the treatment and at frequent intervals throughout the study period to ensure that you are tolerating the therapy. You will have the following assessments performed while you are on the trial:-

Blood tests

Blood tests will be performed on a regular basis. During the first cycle of treatment, you will receive blood tests on day 1 and day 8. For all other cycles, you will have a blood test on day 1 (or (or within 7 days prior to). For the last cycle, these bloods will be performed on or around day 29 (end of treatment visit). These blood tests are to monitor your overall health whilst receiving trial treatment. You will receive a further blood test at the 3 and 6 month post treatment follow-up visits. You may receive additional blood tests throughout the trial if you doctor thinks this is necessary.

Biopsy

You may need a biopsy of the area affected by GvHD as part of the screening process. If a biopsy is necessary, further information will be provided. A skin biopsy may cause minimal discomfort after the procedure; this will be fully discussed with you if it is required. Further samples may be taken during the trial if your doctor thinks this is necessary. You may also be asked during the study for biopsies to be taken from other organs. These will only be to determine if the organ is affected by GvHD and will be completely optional and only if clinically required.

Physical Assessment

A medical assessment (including monitoring your weight, blood pressure, pulse, temperature) will be performed on a monthly basis throughout the trial to assess your overall health whilst participating in this trial. You will also undergo a detailed assessment of the skin and mouth to look at the extent of the symptoms of your cGvHD. Your doctor will also ask you some questions about your overall health. After treatment has finished, this assessment will be repeated at the end of treatment visit and at the 3 and 6 month post-treatment follow-up visits.

Lung Function Tests

Lung function tests will be performed 3 monthly during the trial. These tests will measure various functions of your lungs i.e. lung size, how well they take up oxygen, and if there is narrowing of the airways. These tests are similar to the tests that you would have had done prior to your transplant. Further details of these tests will be explained to you by your study doctor. The tests will take approximately one hour.

Patient Reported Outcomes

You will be asked to complete two short questionnaires about the symptoms of your GvHD on a monthly basis, and again at the 3 and 6 month post treatment follow-up visits. These questionnaires will take no longer than 10 minutes to complete. You may find some of the questions on the questionnaire distressing. If you would like support for any distress caused while completing the questionnaire, please speak to your medical team who will be able to help you.

Quality of Life questionnaires

We are trying to find out how patients with cGvHD feel while on treatment with azacitidine. You will be asked to complete a short questionnaire (in addition to the 2 described above) which will ask questions about how you are feeling and your general well-being. You will be asked to complete the questionnaire on day 1 of each cycle and then again at the 3 and 6 month follow up visits after the end of your treatment. The questionnaire should not take longer than 10 minutes to complete and a nurse will be available if you need help completing it. You may find some of the questions on the questionnaire distressing. If you would like support for any distress caused while completing the questionnaire, please speak to your medical team who will be able to help you.

Samples for research

We are interested in looking at the effects of the treatment on your disease. In order to do this, we require the following samples throughout the trial for use in scientific studies:

- Up to 25 ml (approx. 5 teaspoons) of blood at the start of the study and at the end of each cycle of treatment and at 3 and 6 month visits following the end of treatment (i.e., up to 9 times). These samples will be obtained while you are having your routine samples taken.
- With your consent, a sample from a biopsy you received in the past (routinely stored at your local hospital) will be requested for the study. If your biopsy sample is stored at a different hospital to the one you are being treated at now, we would request it from your previous hospital with your consent. The hospital will need to see a copy of the signed consent form for this study.
- If you are required to have a skin biopsy prior to participating in the trial, a sample of this will also be requested.

Follow up

If at the end of 6 cycles of therapy your disease has improved, you will be able to continue therapy with azacitidine for a further 4 cycles. If you continue to receive trial treatment, you will have the same assessments performed as described above (i.e. physical examinations performed every month and blood assessments). Your Doctor will discuss the most appropriate treatment options with you at the end of the study. Following the end of trial treatment, you will be ask to return to clinic in 3 and 6 months time for the assessments described above.

At the end of your ten month therapy period if all signs of your GvHD have gone, then there will be no further treatment required on trial. If there is a recurrence of your GvHD you will be referred for standard care for GvHD which would comprise of drugs such as steroids, ciclosporin or tacrolimus a type of immunosuppressant.

Expenses and payments

You will not receive any money for taking part in this research study. Transport services may be available at your local hospital. However you would need to discuss access to these with your medical team.

2 What will I have to do?

You will need to attend clinic appointments and undergo the assessments described in this information leaflet. You should make every effort to attend on the scheduled visit days.

You will be given a Patient Card which provides emergency contact details for the trial. You should try and carry this with you at all times and present it to a Doctor if you are admitted to hospital.

Women who are capable of having children and men with partners who are capable of having children will need to take precautions to avoid pregnancy (see section called 'harm to the unborn child').

3 What is the treatment being tested?

Azacitidine
Azacitidine works by blocking the action of a protein called DNA methyltransferase which is a protein that leukaemia cells need to stay alive. Azacitidine has been shown to be effective in some patients with AML by restoring the normal function of the bone marrow. There is also some evidence from smaller trials that azacitidine may be useful in treating GvHD.
Azacitidine is currently licensed for use in patients with MDS, and some types of chronic myelomonocytic leukaemia (CMML) and AML.

What are the alternatives for diagnosis or treatment?
If you decide not to take part in the trial, your doctor will discuss all your alternative treatments with you.

4 Risks and Benefits

What are the possible disadvantages and risks of taking part?
There is always a risk involved in taking any drug. There may be risks of the study drug that are unknown or cannot be predicted at this time, but you will be carefully monitored for any problems. Also, the treatment may not improve your GvHD. During the time you receive treatment you will be examined regularly by the doctor and blood tests will be taken to check for side effects. You are encouraged to ask questions and report anything that upsets you or may be troubling you to your doctor, even if you do not think it is connected to taking the study drug.

What are the side effects of any treatment received when taking part?
The following is a list of the most medically significant or most common side effects reported in completed and ongoing studies considered to be related to azacitidine. As with any other experimental treatment there may be side effects or risks associated with

azacitidine which are not yet known. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Side effects associated with Azacitidine

Very common (a 10% or more chance that this will happen):
Anaemia (a decrease in the number of red blood cells which may make you feel weak or tired); low number of white blood cells with or without fever; a decrease in the number of platelets, the cells that help your blood to clot (thrombocytopenia); a decrease in the number of neutrophils (neutropenia) leading to infections, including pneumonia and urinary tract infections; nausea; vomiting; diarrhoea; stomach pain; constipation; feeling tired, unwell, or weak; fever; sore throat with swelling or pain of the nasal membranes or nose; decreased appetite; pain (including muscle, joints and chest pain); dizziness; headache; shortness of breath with or without exercise; rash; itchiness; bruising, including tiny red or purple spots under the skin or other tissue; injection site reaction, including itching, pain, redness, bleeding, bruising, swelling or damage where the injection/infusion was given.

Common (between a 1% to less than 10% chance that this will happen):
Bone marrow failure which is a severe reduction of red and white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely such as respiratory tract infections; a very severe infection of the blood which may include a decrease in blood pressure; indigestion or upset stomach; pain, swelling, or sores on the inside of the mouth; runny nose; bleeding including from the gums, eye, brain, stomach or rectum (haemorrhoids (piles)); low blood levels of potassium; anxiety; sleepiness; difficulty sleeping; blood in the urine; hair loss; redness of the skin; high blood pressure; low blood pressure; weight loss.

Uncommon (between a 0.1 to less than 1% chance that this will happen):
Allergic reaction (may include skin inflammation, rash, trouble breathing; trouble speaking; fever, and/or diarrhoea); in patients with certain types of cancer.

Rare (less than 0.1% chance that this will happen):
Rapid death of cancer cells, where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage (tumour lysis syndrome). This is very unlikely to occur as you are being treated for cGvHD rather than cancer. Thickening, inflammation, or scarring in the lungs; open skin sores or tissue damage at the site of injection; abnormal kidney function test; kidneys not functioning properly, that has rarely led to too much acid in the blood or kidney failure (sometimes fatal); abnormal liver function may occur that has rarely led to decreased level of consciousness related to liver toxicity (sometimes fatal).

Other Risks
If any physician, other than the Study Doctor, prescribes medication for you for another condition, or you are taking any over-the-counter medications, vitamins, herbal, homeopathic or holistic medications or treatments, you **must** inform the study staff. This is important because the interaction of some medications, vitamins and remedies may cause serious effects, and/or may still be unknown.

While on trial you should not be taking any other drugs which can suppress your immune system, other than steroids, ciclosporin and tacrolimus. You should discuss taking any medication with your Study Doctor and GP.

Please also let your Study Doctor know of any present and past diseases and allergies that you may have had.

Your condition may not get better or may become worse while you are in this study. For more information about risks and side effects, ask your Study Doctor.

Harm to the unborn child
Azacitidine may cause harm to an unborn child if given to a pregnant woman.

Females**:** You cannot take part in this study if you are pregnant or breast-feeding because of the possible risks to an unborn child. If you are a female who can become pregnant, you will be asked to take a pregnancy test prior to starting study drug treatment.

You must agree to use an effective form of contraception during the trial and for at least three months after the treatment has finished. If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately.

Males**:** If your partner might become pregnant you must agree to use an effective form of contraception during the trial and for three months after treatment has finished. If your partner becomes pregnant during the course of the study, we would ask you to tell your study doctor immediately.

What are the possible benefits of taking part?
We hope that you will be helped by taking part in this study, but we can't guarantee this. The information we get from this study may help us to improve future treatments for people who have cGvHD.

What happens when the research stops?
The effect of the treatment on your disease will be monitored at regular intervals. If at the end of 6 cycles of treatment, the doctor feels it is helping you and you are not experiencing any major side effects, the treatment can continue for a further 4 cycles. If you do not complete the trial, or if further treatment is not suitable for you, your doctor will discuss alternative treatment options with you.

What if there is a problem?
If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions. Detailed information is given in Part 2.

Will my taking part be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Information Sheet - Part 2

1 Stopping the trial treatment

What if relevant new information becomes available?

Sometimes during the course of a clinical trial new information becomes available about the drugs that are being studied, for example information about unexpected side effects. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the trial. If you decide to continue in the trial you may be asked to sign an updated consent form.

If new information becomes available, your doctor might consider it to be best to withdraw you from the study. If so he/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the trial?

Taking part in this study is entirely voluntary. You may withdraw from this study at any time. If you decide to withdraw, this will not affect your future medical care. If you wish to withdraw from the study, you should call your study doctor. Your study doctor may ask you to return to the hospital for follow up assessments for safety reasons. If you withdraw, we will still keep records relating to the treatment given to you, as this is valuable to the study.

2 What to do if there are problems

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You can use the contact number at the end of this sheet. However if you'd rather not speak to them directly your local Patient and Advice Liaison Service (PALS) may be able to resolve your complaint informally (if you are treated in England). You can find your local PALS office by asking your hospital or visiting the PALS website (http://www.nhs.uk/chq/Pages/1082.aspx?CategoryID=68&SubCategoryID=153). If you are being treated in Northern Ireland, Wales or Scotland, you should contact your local hospital for an independent advisory service. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of this can be obtained from your hospital. If you are harmed as a result of taking part in this study you may have grounds for a legal action for compensation but you may have to pay your legal costs. NHS Trusts have a duty of care to patients whether or not the patient is taking part in a clinical trial and normal National Health Service complaints mechanisms will still be available to you.

3 Confidentiality

Will my taking part be kept confidential?
All information collected about you for this trial will be subject to the Data Protection Act 1998 and will be kept totally confidential.

Data will be collected from your records and from the information that you provide us. We will capture details such as disease and treatment history, results from the assessments that you undergo and any side effects that are observed during the treatment period.

All information will be stored at the Cancer Research UK Clinical Trials Unit (the Trials Office) at the University of Birmingham on paper and electronically and will only be accessible by authorised personnel associated with the trial. In the Trials Office you will be identified by your initials and date of birth. In addition you will be identified with a unique trial number. In routine communication between your hospital and the trial office you will only be identified by your initials, date of birth, and trial number. A copy of your signed consent form will also be posted to the Trials Office to ensure the correct consenting procedure has been carried out. This will have your name and signature on it.

In addition, anonymised data from the trial will be provided to other 3rd parties (e.g. pharmaceutical companies or other academic institutions) for research, safety monitoring and licensing purposes. This includes researchers at the University of Birmingham to help them analyse the research samples that you have provided.
Safety reports (which include your trial number, initials, date of birth and relevant details of your medical history and treatment) will also be sent to Celgene Ltd (which is the pharmaceutical company that manufacture the treatment being used in this trial). They have the same duty of confidentiality to you as other hospital and AZTEC trial office personnel.

By taking part in the trial you will be agreeing to allow research staff from the Trials Office to look at the trial records, and this includes your medical records. It may be also be necessary to allow authorised personnel from government regulatory agencies, sponsors and/or NHS bodies to have access to information about you. This is to ensure that the trial is being conducted the highest possible standard. These regulatory authorities or research organisations could be within Europe, or outside Europe where the data protection laws may be different. Data sent abroad will not be identifiable.

If you choose to withdraw from the trial treatment we would still like to collect relevant information about your health, as this will be invaluable to our research. If you have any objection to this please let your doctor know.

Under no circumstances will you be identified in any way in any report, presentation or publication arising from this trial.

You can withdraw your consent to our further processing of your data at any time. Under the provisions of the Data Protection Act 1998 you have the right to know what information the Trials Unit have recorded about you. If you wish to view this information please contact Legal Services at the address below. Please note that a small fee may be payable to retrieve this information.

Legal Services
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Involvement of the General Practitioner (GP) /Family Practitioner
We will ask for you to consent to your GP being informed of your taking part in the trial. This is to inform them of your participation in this trial and to ensure there are no medical reasons that they are aware of why your participation in the trial would not be safe. We also send your GP a copy of this information sheet.

4 What happens to the samples?

What will happen to any samples I give?
Anonymised samples of your blood and tissue will be sent to researchers at the University of Birmingham. The researchers will be looking at the effects of the treatment on your cells. This will also involve looking at your DNA.

Any leftover samples may be stored and used for any future ethically approved research.

Will any genetic tests be done?
Genetic testing on your samples will be carried out to assess how cells with different genes respond to treatment.

5 What will happen to the results of the research trial?

The results of the clinical trial will be available after it finishes and will be published in a peer reviewed medical journal. Should you wish to see a summary of the results, or the publication, please ask your study doctor. You will not be identified in any report or publication.

6 Organisation and funding

Who is organising and funding the research?
The University of Birmingham is sponsoring the trial and it is funded by the charity Leukaemia and Lymphoma Research (LLR). Celgene Ltd has also provided azacitidine free of charge. The doctors conducting the trial are not being paid, but a payment may be made to the hospital to cover the costs of the trial tests. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham.

Who has reviewed the trial?
This study has been reviewed by an independent group of people, called a Research Ethics Committee to protect your safety, rights and well-being. It has also been reviewed at your local hospital by the Research & Development Department and the charity LLR.

7 Further information and contact details

If you require any further information or have any concerns while taking part in the trial please contact one of the following people:

<< insert name and contact telephone number of Principal Investigator >>

<< insert name and contact telephone number of Research Nurse >>

<< insert 24 hour emergency contact details >>

You may also find it helpful to contact the following organisations:

Your local Patient Advice and Liaison Service (PALs) (if available locally) who provide advice and support to patients, their families and their carers, website: http://www.nhs.uk/chq/Pages/1082.aspx?CategoryID=68&SubCategoryID=153 (patients treated in England only).
Or local advisory service details where available:
<< insert address and contact telephone number of local service >>

CancerHelp, an information service about cancer from Cancer Research UK, Freephone 0808 800 40 40, website: www.cancerhelp.org.uk

Macmillan Cancer Support: Freephone 0808 800 0000, www.macmillan.org.uk

If you take part in this study you will be given a copy of this information sheet and a copy of the signed consent form to keep.