**Study title:** Blinatumomab in molecular relapse of AML with a t(8;21) translocation

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**Patient information sheet (PIS) – version 1.0, 9th May 2021**

**Invitation and brief summary**

We would like to invite you to take part in a research study (also called a clinical trial). Joining the study is entirely up to you; before you decide we would like you to understand why the research is being done and what it would involve for you. Please take time to read this information carefully and discuss it with others if you wish. We encourage you to ask any questions that you may have.

Your doctor has invited you to consider taking part because you have been diagnosed with acute myeloid leukaemia (AML) with translocation 8;21 (explained further in the section below) and have received chemotherapy. Blood or bone marrow tests have shown that you are in remission (no leukaemia cells seen under the microscope), but that very low levels of disease are still detectable. Your doctor feels that further therapy is required to eradicate the leukaemia. A novel treatment called blinatumomab is being tested as an alternative to intensive chemotherapy. Patients treated with this new therapy will be closely monitored and if the treatment is not working will be rapidly moved to a standard chemotherapy approach.

**What’s involved?**

Acute myeloid leukaemia (AML) is usually treated with intensive chemotherapy, and sometimes a stem cell transplant, in the hope of eradicating the disease. Unfortunately, in a proportion of patients the disease will return, referred to as relapse. In some types of AML, specialised genetic tests can be used to monitor for very low levels of leukaemia, which may be present even if no leukaemia can be seen in the blood or bone marrow when examining with a microscope. This is known as minimal residual disease (MRD), and its detection can identify patients who are at high risk of future relapse.

This trial focusses on a subtype of AML where there is a specific genetic abnormality in the leukaemia cells. Two pieces of genetic material, known as chromosomes, are rearranged and join together abnormally. In this type of AML, parts of chromosomes 8 and 21 join together and form what is known as translocation 8;21 or t(8;21). This subtype accounts for 8-10% of cases of AML. When the chromosomes join together, an abnormal gene is produced which is called *RUNX1-RUNX1T1*. This gene can be used as a marker of MRD. We know that a patient with detectable *RUNX1-RUNX1T1* in the bone marrow or blood is likely to suffer disease relapse and would normally be recommended to have further intensive chemotherapy and possibly go on to a stem cell transplant. While this treatment is potentially curative, it is also highly toxic with significant short-term and late side effects.

The BlinAML study is designed to test the effectiveness of a new treatment approach in patients with AML with translocation 8;21 who have previously received chemotherapy but have either persisting, or increasing MRD levels. The therapy is an antibody called blinatumomab, which is specifically designed to target cells with a marker on their surface known as CD19. CD19 is almost always present on AML cells with translocation 8;21. Blinatumomab has a unique mechanism of action, bringing leukaemia cells in contact with immune cells known as T cells, which can then kill the leukaemia cells. Blinatumomab has been widely used in other types of leukaemia and lymphoma but not in AML.

The aim of the BlinAML study is to determine if blinatumomab can effectively eradicate low levels of leukaemia, sparing patients the side effects of intensive chemotherapy. If you agree to take part, you will receive 1 to 4 cycles of therapy. Your response will be closely monitored and if the treatment is not working you will be able to rapidly move to a standard chemotherapy approach. After treatment with blinatumomab, your doctor may recommend further therapies, which may include a stem cell transplant. The trial will not alter the way this decision is made .

**What would taking part involve?**

Consent and Screening

If you decide to take part in this study, we will ask you to give your written informed consent to take part and the following tests will be performed to make sure you are suitable for the study.

* A medical history, including medicines you currently take
* A physical examination and vital signs assessment
* An examination of your neurological system including a writing test
	+ The writing test involves writing a simple sentence on a piece of paper
* A pregnancy test (if you are a female of child bearing potential)
* Blood tests – we will collect information about the results of several different tests as part of this study, including blood counts, liver and kidney function and evidence of previous exposure to viruses (such as hepatitis and HIV). We will require approximately 30mL of blood for these tests
* Electrocardiogram (ECG), a non-invasive test of the electrical conduction systems of your heart
* A urine test
* Bone marrow aspirate and biopsy for disease assessment.
* A discussion regarding contraception requirements – at least one form of highly effective contraception will be required during and for 3 months after the study (further information below)

You will need to have most of the tests described here as part of your treatment, whether or not you decide to enter this study.

What will happen during the study?

If you are eligible and agree to enter the study, you will receive 1 to 4 cycles of blinatumomab therapy. Each treatment cycle is 6 weeks. Blinatumomab is given to you through a vein (intravenous) continuously for 4 weeks, followed by a 2-week break. Hospital admission is only required for 2 to 3 days of each cycle.

The table below gives a description of the assessments required for this study. You would have most of these assessments as part of your routine care, whether or not you decide to enter this study.

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| **Time point in the cycle** | **Tests or Procedures** | **Amount of time taken** |
| Days 1, 2, 3 then weekly during each cycle  | * Full physical examination, vital signs and writing test
* Blood tests (approximately 30mL of blood each time)
* Assessment for side effects of treatment
 | 30 minutes |
| Day 29 of each cycle (end of treatment) | * Full physical examination, vital signs and writing test
* Blood tests (approximately 30mL of blood)
* Assessment for side effects of treatment
* Bone marrow aspirate (including biopsy if required) to assess response to treatment.
 | 30 minutes+ 30 minutes for bone marrow |
| **Follow-up period – after treatment is completed**  |  |
| 90 days after final infusion completed  | * Full physical examination, vital signs and writing test
* Blood tests (approximately 30mL of blood)
* ECG, urine test, pregnancy test (women of childbearing potential)
* Assessment for side effects of treatment
 | 30 minutes |
| 3 monthly for 1 year, 6 monthly for the second year\* | * Full physical examination, vital signs and writing test
* Blood tests (approximately 30mL of blood)
* Assessment for side effects of treatment
* Bone marrow aspirate (including biopsy if required) to assess for relapse.
 | 30 minutes+ 30 minutes for bone marrow |
| \*These visits are not needed for patients who have a stem cell transplant |

We will collect information about you and your disease, how it responds to treatment and any side effects you experience for 2 years after the end of your treatment. This is to understand whether there are any unexpected long-term effects of the therapy.

How will the treatment be given?

You will be admitted to hospital for the first 3 days of cycle 1 and the first 2 days of subsequent cycles. This is to monitor closely for any side effects associated with starting the treatment. Some patients may require longer hospital stays. Blinatumomab is giving intravenously (into your vein) as a continuous infusion for 28 days. This will require a central venous catheter (CVC) to ensure reliable access to a vein. Prior to the start of the blinatumomab you will receive intravenous dexamethasone, a corticosteroid designed to reduce treatment side effects.

If you do not experience significant side effects from the treatment, you will be discharged home for the remainder of the cycle. The blinatumomab will remain connected to your CVC to allow for a continuous infusion. The medication will be loaded into a Continuous Ambulatory Delivery Device (CADD) pump (see image below). You will be provided with an infuser bag and be instructed in how to carry it and care for it. You will also be provided with contact details in case of any issues that arise at any time. You should not disconnect or stop the infusion at any time.

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| *Figure 1 – picture of CADD pump* |

You will have weekly assessments in the outpatient unit by the trial medical team during the 28-day infusion. You will be provided with contact details in case of any side effects, and will be able to be reviewed urgently if needed. After the infusion is disconnected, you will have at least two weeks’ break between cycles.

Bone marrow tests

Having bone marrow tests is an essential part of monitoring your response to treatment. There are two types of bone marrow tests: bone marrow aspirate and bone marrow biopsy.

* A bone marrow aspirate is the removal of a small sample of liquid bone marrow.
* A bone marrow biopsy is the removal of a small solid piece of bone marrow which is about the thickness of a pencil lead and about 1-2cm (half an inch to an inch) long.

After each cycle of treatment, you will usually only have a bone marrow aspirate however your doctors might need to do a biopsy as well in certain situations. All your bone marrow samples will be tested using a very accurate method called a minimal residual disease (MRD) test. This test can usually detect one leukaemia cell mixed in with a million normal cells.

Whether or not you enter this study, you will need to have both types of bone marrow sample taken before starting treatment and during follow-up. The number of bone marrow tests taken as part of the trial will not be more than you would have as part of standard care.

What are the alternatives to taking part?

Your doctor has determined that you require treatment to try to eradicate the leukaemia from your bone marrow and blood. The standard treatment is intensive chemotherapy, with a combination of drugs given intravenously over a number of days. The most common regimens are known as FLAG-Ida or FLAG, of which 1 – 2 cycles are given over a couple of months. These treatments cause blood counts to drop significantly and require an average of one month in hospital. Up to 10% of patients require admission to an intensive care unit and around 5% die from complications of therapy, mainly due to infection.

Patients who receive chemotherapy and attain a remission may be offered a stem cell transplant to reduce the risk of future relapse. This is the case both for patients in the trial and those treated with standard therapies. Your doctor will consider whether you are eligible for a transplant and discuss this further with you.

**What are the possible benefits of taking part?**

There is no guaranteed benefit to taking part in this study because we do not yet how effective blinatumomab is in this situation. The careful monitoring you will receive if you take part in this study is a safeguard against this risk. If the therapy is not working, you will be able to quickly change to standard chemotherapy.

As blinatumomab is likely to be less toxic than standard chemotherapy, it is possible that patients receiving this treatment may experience fewer side effects. The information gained from this study will help improve treatment for other people with AML in the future.

**What are the possible disadvantages and risks of taking part?**

What are the side effects of treatment?

Blinatumomab is not chemotherapy and has a unique set of side effects. In the majority of cases these are manageable with medications and temporary interruption or dose reduction of the infusion. If side effects are very severe, it is possible the treatment will need to be permanently stopped. Most of these side effects have been reported with blinatumomab are in patients with a large amount of disease. Only patients with minimal residual disease are eligible for this trial and such patients are much less likely to get these side effects

*Neurological side effects*

Blinatumomab has been associated with neurological (brain and nervous system) side effects. These tend to occur in the first two weeks of treatment and the majority resolve. Symptoms can include dizziness, changes in alertness, confusion and/or disorientation, difficulty speaking or slurred speech, difficulty understanding words, shaking, difficulty walking, loss of balance, abnormal sensations, memory loss, loss of consciousness or seizures. In a previous trial of a different type of leukaemia where blinatumomab was used for MRD, significant neurological toxicity occurred in 13% of patients. You will be monitored closely for these effects and if they occur you may receive medications such as steroids or potentially have the blinatumomab infusion paused or stopped.

*Cytokine release syndrome*

Cytokine release syndrome (CRS) refers to a collection of symptoms that occur due to activation of a patient’s immune system. These signs and symptoms of cytokine release syndrome occur in the first few days of treatment and are generally mild to moderate but occasionally can be serious or life threatening. Symptoms of CRS include fevers, fatigue, headache, low blood pressure and blood test abnormalities. In a previous trial of a different type of leukaemia where blinatumomab was used for MRD, CRS occurred in only 3% of patients. You will be monitored closely for these effects and if they occur you may receive medications such as steroids or potentially have the blinatumomab infusion paused or stopped.

*Other side effects*

Side effects that have been seen in at least 1 in 10 participants (very common) include:

* Infection – both AML and the treatment will make you more susceptible to infection. Your doctor will instruct you about the steps to be taken if you develop a high temperature. If you do develop a temperature this can quickly turn into a life-threatening infection without prompt treatment, so it is important that you receive medical attention and antibiotics straight away.
* Decreased blood levels of white blood cells, red blood cells, and platelets
* Abnormalities in liver function tests
* Rash
* Abdominal pain, diarrhea or constipation
* Chest pain
* Cough
* Bone, joint or back pain
* Swelling of hands, legs, ankles, feet, face, or trunk
* Increased level of blood sugar, and decrease in magnesium and/or decrease in potassium level in the blood

Side effects that have been seen in at least 1 in 10,000 participants (rare) include

* Increased heart rate
* Decreased levels of blood immunoglobulins
* Decreased levels of albumin in the blood
* Tumour lysis syndrome – unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures
* Leukoencephalopathy – symptoms can include difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision

Potential side effects of any medication:

* Allergic reactions – sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction, you might develop a rash, difficulty breathing, wheezing when you breathe, sudden low blood pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating. Before starting the study drug, you must tell your Study Doctor about any drug allergies. You should tell the Study Doctor right away if you have any allergy symptoms listed above.
* Fatigue – if you are affected by fatigue caution must be exercised when driving or using heavy machinery. Do not carry out these activities if you feel it is not safe to do so.

You should tell your study doctor or medical team about any side effects that you have, even if you do not think they are connected to the drugs. Your doctor may be able to give you medications to help treat the side effects and prevent them from becoming worse. All side effects will be monitored closely to minimise any risks to you. Your study doctor may also choose to stop or delay treatment for a short time or reduce the dose to allow you to recover from any side effects.

Harm to the unborn child

*Information for women*

Blinatumomab may cause harm to an unborn child if administered during pregnancy. There is little or no information of the effects on the child when breast feeding during treatment. You cannot take part in this study if you are pregnant, breast-feeding, planning to become pregnant or to do an egg donation while receiving blinatumomab or until 3 months after blinatumomab discontinuation. If you are a female who can become pregnant, you will be asked to take a pregnancy testprior to starting study drug treatment.

If you decide to take part in this study, you must agree to use at least one form of highly effective contraception without interruption (see box below).

If you become pregnant while receiving blinatumomab or until 3 months after blinatumomab discontinuation, you must tell your doctor right away and any study medication you are taking will be discontinued. Your doctor will explain how to safeguard your health and the health of your baby. If you agree, we will collect information related to the progress of your pregnancy and its outcome that is relevant to the study. This may include information related to your health, the date of conception, the course and outcome of your pregnancy and any medical treatments that you receive.

*Information for men*

If you were to father a child, the treatments you will receive as part of this study may be harmful to the unborn child. Your doctor will talk to you about potential sperm donation before you start treatment and you should not be involved in sperm donation during this time. If your partner might become pregnant you/your partner must agree to use at least one highly effective form of contraception during the trial treatment and for 3 months after blinatumomab discontinuation.

If your partner becomes pregnant during the course of the study, we would ask you to tell your study doctor immediately and your doctor will ask you and your partner for permission to collect information about the pregnancy and the child. Your doctor will explain to you and to your partner how to safeguard your partner’s health and the health of the baby.

The acceptable methods of effective contraception are: combined hormonal contraception or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion (a surgical procedure that involves blocking the fallopian tubes), a vasectomised partner, or sexual abstinence.

**Please speak to your study doctor who will be able to provide appropriate contraception advice.**

What food/medications (additional medication) should I avoid?

It is very important that you tell the study doctor about all medications, supplements, or herbal medicine that you are taking now and during the study. Even herbal medicines and other alternative treatments can interact with medications, and these interactions could be dangerous.

**Further supporting information**

Will I be paid to take part?

You will not receive any money for taking part in this study and unfortunately travel expenses cannot be reimbursed by the study organisers. However other transport services may be available. Please discuss access to these with your medical team.

What if relevant new information becomes available?

If we get new information about the treatment being studied, your doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your doctor will make arrangements for your care to continue. If you decide to continue in the study your doctor may ask you to sign an updated Informed Consent Form. If new information becomes available your doctor might consider that you should withdraw from the study. Your doctor 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 so you receive the best care available.

What if I want to withdraw from the study?

You are free to withdraw from the study at any time, for any reason. If you choose to withdraw, your clinical care will not be affected in any way. Any information we have about you from the time you were in the study will be kept and included in the analysis of the trial. We would also like to continue collecting information about your health from your treating haematologist. If you do not want this to happen, tell us and we will stop.

What will happen to my samples during and after the study?

All samples collected during the study will be analysed and stored on site at Guy’s Hospital, using the laboratory tests which would be performed as part of routine clinical care. There are no additional or surplus sample requirements.

We will need to keep samples of blood and bone marrow until the end of the study for all patients in case there are any discrepancies in the results and re-testing is needed. After this time, the samples will be stored for as long as is required by guidelines governing standard laboratory practice.

Involvement of the General Practitioner (GP) / Family Practitioner

It is important that your GP is kept up to date with any treatment you are receiving. Your GP will be informed that you are taking part in this research study and they will be sent a copy of this information sheet.

What will happen to the results of the study?

When the study is complete the results will be published in a medical journal but no individual patients will be identified. If you would like to have a copy of the published results, please ask your study doctor or nurse.

Will any genetic tests be done?

Yes. Genetic studies are performed on your leukaemia cells to confirm the presence of the *RUNX1-RUNX1T1* gene abnormality. This is a test which is routinely performed for patients with your type of AML. In addition to genetic testing at screening, researchers will also monitor the level of tumour cells in your bone marrow to see if you are responding to treatment. Results and data from analysing the samples as part of the study will be returned to your local doctor and used to guide your medical care. These tests only look for genetic changes which occurred during your life-time. They do not look for inherited genetic problems and so these results will not have consequences for your family members.

Who is organising and funding the study?

This research is being funded by Amgen, who are also providing blinatumomab for the study Guy’s and St Thomas’ NHS Foundation Trust are the study sponsors. The study is being run at Guy’s Hospital.

Who has reviewed the study?

This research study has been reviewed by Guy’s and St Thomas’ NHS Foundation Trust R&D Departmentand also by an independent NHS Research Ethics Committee (REC). RECs review all research to protect the safety, rights, wellbeing, and dignity of participants. This study was reviewed and received favourable opinion by <insert when known> Ethics Committee. It has been reviewed and received a Clinical Trial Authorisation by the UK Competent Authority (Medicines and Healthcare products Regulatory Agency - MHRA) It has also been reviewed by the national Health Research Authority and two Patient Representatives.

**Information on the Use of Data**

How will we use information about you?

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

This information will include your initials and date of birth. People will use this information to do the research or to check your records to make sure that the research is being done properly. The records will be reviewed by representatives of the trial sponsor who are not employees of the NHS Trust.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep the data for 5 years 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.

What are your choices about how your information is used?

* You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
* If you choose to stop taking part in the study, we would like to continue collecting information about your health from your treating haematologist. If you do not want this to happen, tell us and we will stop.
* 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.

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

You can find out more about how we use your information

* at [www.hra.nhs.uk/information-about-patients/](https://www.hra.nhs.uk/information-about-patients/)
* our leaflet available from: [www.guysandstthomas.nhs.uk/research/patients/use-of-data.aspx](http://www.guysandstthomas.nhs.uk/research/patients/use-of-data.aspx) (For GSTT) and [www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research](http://www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research) (for KCL)
* by asking one of the research team (contact details included below)
* by contacting the Data Protection Officer: (For GSTT: Nick Murphy-O’Kane DPO@gstt.nhs.uk; For KCL: Albert Chan info-compliance@kcl.ac.uk)

**What if there is a problem?**

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 [insert Principal Investigator name, telephone number and e-mail address]. If you remain unhappy and wish to complain formally, you can do this through the Guy’s and St Thomas’ Patients Advice and Liaison Service (PALS) on 020 7188 8801, pals@gstt.nhs.uk. The PALS team are based in the main entrance on the ground floor at St Thomas’ Hospital and on the ground floor at Guy’s Hospital in the Tower Wing.

In the event that something does go wrong and you are harmed during the research and this is due to someone‘s negligence then you may have grounds for legal action for compensation against Guy’s and St Thomas’ NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).