Patient Information Sheet

SPIRIT 2

STI571 Prospective International Randomised Trial 2

A phase III, prospective randomised comparison of

- **imatinib** (STI571, Glivec/Gleevec) **400mg daily** versus
- **dasatinib** (Sprycel) **100mg daily**

in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

We would like to ask you three questions;

1.) Would you be interested in joining a clinical research study aimed at improving the treatment of CML (SPIRIT 2)?
2.) Would you donate a small amount of your blood for research projects both now and in the future aiming to improve the treatment of chronic myeloid leukaemia?
3.) Can we collect and hold information about you and your illness (a 'registry') on a computer system so that we can better understand how common CML is and what happens to people with the illness. Such a registry would also allow us to contact you about new treatments in the future if you wish.

You don't have to agree to any of these requests or you can agree to some but not others: there are three separate consent forms at the end of this document which will allow you to indicate your preference.

1. SPIRIT 2: a study looking at two drug treatment options for CML patients

You are being invited to take part in a research study (clinical trial). Before you decide whether or not to take part in this study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Do ask us if there is anything that is not clear or if you would like more information. Please take your time to decide whether or not you wish to take part.

Until recently interferon was the standard treatment for CML. A new drug called imatinib (STI571, Glivec®) has been developed for use in this disease and is now the standard treatment for CML. Imatinib has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for treating newly diagnosed patients with CML like yourself.

Recently a new drug called dasatinib (Sprycel) has been approved by for the MHRA for use in people with CML who have already been treated with imatinib. Dasatinib has not been used in many people with CML as the first treatment they receive after they are diagnosed.

This study is designed to compare the standard treatment, imatinib 400mg, with dasatinib 100mg in patients who have not received any previous treatment like yourself. New information is now available from a recent study using dasatinib as first option for the treatment of newly-diagnosed patients. The data are very encouraging but there are no long term data to indicate that survival is better (for example at five years) compared with imatinib. In SPIRIT 2 we are trying to work out whether there is any difference in long-term survival between imatinib and dasatinib.

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).

A computer will randomly allocate the treatment that you will be given – either i) imatinib 400mg daily or ii) dasatinib 100mg daily. An equal number of patients will get each treatment.

What is the purpose of this study?

The purpose of this study is to investigate over five years whether dasatinib 100mg/day is better than imatinib 400mg/day at improving survival. Additionally the tolerability of the treatments will be compared.

We will also be looking at your 'molecular response' to treatment after one year. This is a very sensitive laboratory measure of how much leukaemia is left after one year on treatment.

The overall aim of the project is to find out if dasatinib is a better treatment than imatinib for the treatment of chronic myeloid leukaemia which may give doctors and future patients a choice of treatments.

Why are we asking you to participate?

In light of the experience to date, we think you may benefit from one of the treatments. Furthermore, you fulfil certain other inclusion criteria, e.g. your general status of health as well as your prior treatment match the criteria set out in the study protocol.

Do you have to participate?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. If you should decide not to participate you will receive the best current treatment available at our Hospital.

What if you do decide to take part?

At your initial visit we will note your disease history, will ask you what drugs you currently take, take some blood tests and a bone marrow sample. At the subsequent visits we will ask you how you feel, ask you to complete a health questionnaire, we will take blood samples and occasionally a bone marrow sample. From time to time we will examine you thoroughly.

If you meet all the criteria you will be randomly assigned to one of two treatments:

1. imatinib 400mg
   You will be given imatinib to be taken by mouth at a starting dose of 400mg each day.

2. dasatinib 100mg
   You will be given dasatinib to be taken by mouth at a starting dose of 100mg each day.

The study will last for five years. You will have a bone marrow biopsy at study entry, and then every year. You will need to give blood samples once a month for the first three months, then every three months for the remainder of the first year. Thereafter you will need to give blood samples every six months. You will have a physical examination at the same time you visit to give these blood samples. You will be asked to complete a health questionnaire at the start of the study and then every month for the first three months and then at six and twelve months and then once a year until the end of the study.

Some of the blood from the routine blood samples will be used for testing your molecular response.

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, we will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Please note: on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

How long will I take the study drugs for?

In light of current evidence, it is likely that you will need to continue drug treatment for CML indefinitely. However, you will receive treatment as part of this study for a minimum of 5 years.

The National Institute of Clinical Excellence (NICE) have approved imatinib for first line treatment of CML. If you are assigned to receive 400mg daily imatinib, the National Health Service will provide you with a daily supply of 400mg imatinib indefinitely. If you are assigned to the 100mg/day dasatinib group the dasatinib will be paid for by the pharmaceutical company Bristol Myers Squibb. Dasatinib will be provided for each patient for 5 years after the last patient is recruited into the study. This means if you are the first patient recruited into the study and we recruit the last patient 3 years later you will be provided with dasatinib for a total of 8 years. However if you are the last patient recruited into the study you will only be guaranteed a supply of dasatinib for a total of 5 years.

Therefore, if you are assigned to the 100mg/day dasatinib group, depending at what point in the study you enter the supply of dasatinib is not guaranteed for longer than 5 years treatment for you. After the end of the study it is possible that dasatinib may be available and funded through the NHS but it is not possible to guarantee this at present. We believe that, if necessary, switching to 400mg daily of imatinib after 5 years would continue to provide you with highly effective ongoing therapy for your leukaemia. However, there may be further developments in treatment in the future which may mean that you need to switch to another type of treatment.

What do you have to be careful about if you take part?

As with any new drugs, you have to be wary of taking any additional medications, including common drugs such as paracetamol and aspirin (which are also often contained in 'cold' remedies), whilst participating in this study. Please do not take ***any*** new medications before first checking with your study doctor/nurse.

If there is a possibility that you could become pregnant or father a child during the course of treatment then you must use a barrier method of contraception (e.g. a condom or diaphragm) as well as your normal method of contraception if this is different. This is due to the fact that imatinib and dasatinib are cell-killing drugs. Dasatinib is suspected to cause congenital malformations including neural tube defects (eg. spina bifida), and other harmful effects on the foetus when administered to pregnant women. There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown reproductive toxicity and the potential risk for the foetus is unknown
You should avoid becoming pregnant or fathering a child whilst on this study.

What are the risks of participation?

Imatinib is known to be a highly effective treatment for CML. If you decide to take part in this study you will have a 50% chance (1 in every 2 patients) of receiving dasatinib instead of imatinib. Dasatinib is a newer drug and so we know less about it. We don't know if dasatinib will work as well as imatinib which is one of the reasons we are doing this study.

Many patients who take imatinib or dasatinib have no side effects at all. The common side effects with these medicines are usually mild and easily treated. Sometimes a change of dose is required.

The possible side effects of treatment with **imatinib** are fatigue, muscle cramps, indigestion, diarrhoea nausea, oedema (excess fluid, especially around the eyes and ankles), rash and headache usually of mild to moderate nature. Rarely, changes in some of your liver function values and a reduction in your blood counts below normal values can occur which is why we have to take frequent samples of blood. If any of these or other side effects occur during this study, they should be reported to the study doctor or nurse.

The potential side effects of treatment with **dasatinib** are fluid retention (including pleural effusion - excess fluid in the space surrounding the lungs), skin rash, headache, haemorrhage (bleeding), fatigue, diarrhoea, nausea, shortness of breath and muscle and joint pain. Dasatinib can make your blood counts go too low which is why we have to take frequent samples of blood. A very small number of patients taking dasatinib have been found to have Pulmonary Arterial Hypertension (PAH) (this is high pressure in the artery between the heart and the lungs). Patients with PAH usually have mild shortness of breath. Although it is not

certain whether dasatinib causes PAH, in patients on dasatinib where PAH has been suspected the condition has gone away when the drug was stopped. As shortness of breath can be caused by a number of medical conditions you should **tell your doctor if you experience unusual shortness of breath during gentle activity** (e.g. walking upstairs) and they will be able to investigate the cause. All other side effects should also be reported to the study doctor or nurse.

Imatinib and dasatinib are mainly handled by the liver. Some other medicines also affect the liver and should not be used with imatinib or dasatinib without consulting your doctor:
Some of these medicines include:

- ***ketoconazole, itraconazole*** - these are **antifungal medicines**
- ***erythromycin, clarithromycin, telithromycin*** - these are **antibiotics**
- ***ritonavir*** - this is an **antiviral medicine**
- ***dexamethasone*** - this is a **corticosteroid**
- ***phenytoin, carbamazepine, phenobarbital*** - these are treatments for **epilepsy**
- ***rifampicin*** - this is a treatment for **tuberculosis**
- ***famotidine, omeprazole*** - these are medicines that **block stomach acids**

Please tell your doctor if you are taking these or any other medicines, or have recently taken any. This includes **medicines to thin the blood** or prevent clots; it also includes medicines obtained without a prescription, such as **herbal medicines (e.g. St. John's Wort)**.

What if something goes wrong?

Please contact us immediately if you have concerns about any aspect of this study or your health. Whilst we do not anticipate any major problems one cannot predict every eventuality. If taking part in this study harms you there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the National Health Service complaints mechanisms are available to you.

What about confidentiality?

All information which is collected about you during the course of the research will be kept strictly confidential. If you agree to take part in the study, a copy of your signed consent form, containing your full name, will be sent to the SPIRIT Trial Manager either by fax or post.

If you consent to take part in this trial any of your medical records may be inspected by members of the trial monitoring team for purposes of analysing the results. People may also look at them from regulatory authorities to check that the study is being carried out correctly.

If you so wish, we will inform your GP and/or any other medical practitioner who currently treats you about your participation in this study.

All data collected during this trial will be processed in accordance with the Data Protection Act, 1998. Personal details such as your initials, date of birth, NHS number and data collected during the trial will be entered onto a computer and stored electronically. Responsible individuals from the trial team will access this information. If you wish, you will be able to access your own trial information over the web using a personal username and

password. You will be able to check that personal details about you are correct and see your own results and progress in the trial. No other patient will be allowed to see your records and you will not be allowed to see anyone else's.

What are we going to do with the study results?

The study results will help us to know whether dasatinib is useful in treating newly diagnosed patients with CML and how it compares to 400mg imatinib. In this way we seek to continually improve the treatment of patients with CML. We may aim to publish the results at scientific meetings and in journals to allow discussion and evaluation of these results amongst our peers. The pharmaceutical company that makes dasatinib (Bristol Myers Squibb) may also use the study results to apply for approval for use of dasatinib in other newly diagnosed patients.

The study is Sponsored by the Newcastle upon Tyne Hospitals NHS Trust with funding from the pharmaceutical company Bristol Myers Squibb. No payments will be made to your doctor during the course of this study.

The study has been reviewed and approved by the London Research Ethics Committee.

Your study contacts: Dr. A, Research Nurse B.

Finally, if you proceed, we would like to thank you for agreeing to take part in this study. Please keep a copy of this information sheet for your records. You will also receive a copy of your signed consent form.

2. Donating of blood for use in research projects

What material do we want to collect?

We would like to collect a small amount of blood from you at the same time as your blood is being taken for routine blood testing. This blood will be used to extract plasma, cells and genetic material such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). We would like to collect this material at regular intervals during the course of your treatment. We may also collect a small amount of bone marrow from you at the time that you have your routine bone marrow tests.

How will the material be stored?

This material will be processed, frozen and added to a biobank, which consists of frozen material from other newly diagnosed CML patients like yourself. Depending on where you live this material may be stored at a different hospital to this one and may be shipped abroad during the course of research projects in collaboration with other groups. You will be asked to donate the material freely and you will have no claims on this material at any time in the future. You will not be informed of the outcome of any of the research involving your material.

What will we do with the material?

The aim is to collect the material and use it to answer specific research questions relating to your disease at some time in the future. Your material may be used by other doctors and by commercial companies to develop better tests or treatments. Samples will be collected regularly throughout the study.

You will be asked to consent to this material being used in this way. The consent form will be separate to the one you will be asked to sign if you participate in the SPIRIT study.

Why is this material being collected?

Various research groups in the UK and around the world are seeking to understand the biology of chronic myeloid leukaemia in order to develop better tests to diagnose and monitor the disease and in order to develop better treatments. The samples you donate will be used by a number of different researchers both in the academic and commercial sectors to help with this research.

Who will ensure that the material will be used for ethically approved purposes only?

There are a number of existing research projects that your samples will help. However we don't know what questions we might want to ask in a few years time and we are seeking your permission to use your samples for existing projects and also for projects that come up in the future. We are therefore asking you to donate your samples to the research community. This means that in the future we can use your samples for new research projects without coming back to you to ask your permission over and over again. Your samples will only be used in these future projects after careful review and approval by a Research Ethics Committee (REC).

What about confidentiality?

Your samples and information such as your initials, date of birth, NHS number, medical history and CML treatment will be held securely on a password protected database. Your information will only be released to researchers for specific projects that have received the appropriate approvals (i.e. ethical and regulatory). Samples will be anonymised and identified by a unique study number only, your full name and address will not be kept with the sample and will not be shared with researchers. Information about you or derived from your samples will not be shared with any outside agency such as the police, insurance companies or your employer unless you give your specific instruction/permission for us to do so or we are compelled to release the information under common law.

3. Registry of information about patients with CML

Why do we want to collect information about you for a 'registry'?

We wish to collect information about you and your illness to better help us understand the nature of CML, how common it is, how people with the illness are treated and how well they do on current forms of treatment. This will help us understand the illness better and help researchers work towards a cure for most patients.

What information do we want to collect?

We want to know basic information about you including your full name, address, email and phone number so that we can contact you about any developments in the field of CML. This information will be stored on a secure, password protected database. Only that database administrators will have full access to your personal details and where for example a laboratory researcher wishes to invite you (and/or a sample from you) to join a research project, your information will be 'anonymised' so that you cannot be identified. For example you would be referred to as "BJ, DOB 14/3/47" rather than Brian Jones, 16 Acacia Avenue, Birmingham". This anonymisation is to preserve your privacy as much as possible.

What if I change my mind?

If you change your mind at any stage in the future you will be able to ask for your information to be deleted from the computer system or to remove your personal details and remain completely anonymous if you wish.

Contacting you about research progress and developments in CML.

Finally we want to keep you informed regularly about developments in the treatment of CML. We would like your consent to contact you from time to time to let you know about new developments, new studies you may be interested in participating in and also to keep you informed about progress of the research projects being described in this document. The frequency with which we will contact you will depend on the number of new studies that come up and the amount of new information available but we will ensure that it is not excessive – possibly 2 or 3 contacts per year.

Participant Consent Form

1. Participating in the SPIRIT 2 trial

STI571 Prospective International Randomised Trial 2

A phase III, prospective randomised comparison of

- **imatinib** (STI571, Glivec/Gleevec) **400mg daily** versus
- **dasatinib** (Sprycel) **100mg daily**

in patients with newly-diagnosed chronic phase
chronic myeloid leukaemia

The participant should complete the whole of this sheet him or herself.
(Please write your initials in the following boxes if you agree with the statement)

		Please **initial** here ↓
1.	I confirm that I have read and understood the information sheet dated 02 November 2016 for the above study and have had the opportunity to ask questions.	
2.	I understand that I am not eligible to enter SPIRIT2 trial if I am pregnant. I have been informed of the risks and have been advised not to get pregnant or father a child whilst taking the study drugs.	
3.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without it affecting my medical care or legal rights.	
4.	I understand that sections of any of my medical notes may be looked at by responsible individuals from the trial team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
5.	I understand that personal data such as my initials, date of birth, hospital/NHS number and data collected during the trial will be entered onto a secure computer system and stored electronically. I give permission for responsible individuals from the trial team to access this information.	
6.	I understand that this information is password protected and that I may be supplied with a username and password to allow me to access this information.	
7.	I understand that a copy of my signed consent form, containing my full name, will be sent to the SPIRIT 2 Trial Manager either by fax or post.	
8.	I agree to my General Practitioner being informed of my participation in the study.	
9.	I agree to take part in the above study.	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes

Participant Consent Form

2. CML BIOBANK

Donation of material taken during routine sampling

The participant should complete the whole of this sheet him or herself.
(Please write your initials in the following boxes if you agree with the statement)

	Please **initial** here ↓
1. I confirm that I have read and understood the information sheet dated 24th October 2014 for the SPIRIT 2 study and donation of research samples and have had the opportunity to ask questions regarding the storage of material (taken during routine blood sampling) into a biobank.	
2. I understand that material obtained from routine samples of blood and marrow is given freely as a donation and that I will not retain any rights to the material in the future.	
3. I understand that this material will be frozen and added to a biobank. The material in the biobank will be shared with other doctors or commercial companies and used to answer specific research questions relating to my disease.	
4. I understand that I will not be informed of the results of any research project using my material.	
5. I consent to personal information about me, my initials, date of birth, hospital/NHS number my disease and treatment history and my research samples being held on a computer database that will be held securely and may be accessed by other appropriately authorised researchers in the UK and abroad.	

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes

Participant Consent Form

3. Registry of CML patients

Collection and analysis of information about you and your illness aiming to improve the treatment of CML and keep you informed

The participant should complete the whole of this sheet him or herself.
(Please write your initials in the following boxes if you agree with the statement)

	Please **initial** here ↓
1. I confirm that I have read and understood the information sheet dated 24th October 2014 for the SPIRIT 2 study and collection of information for a registry and have had the opportunity to ask questions regarding the information to be collected about me	
2. I understand that my name, date of birth, NHS number, address, phone numbers and email address as well as details about my illness will be entered onto a computer system and accessed by limited numbers of medical researchers. I understand that this information will not be given to any third parties including commercial companies or government agencies without my specific consent. I consent to such information being collected about me.	
3. I would like to be kept informed about the progress of research in CML and agree to researchers contacting me in writing to invite me to participate in future research studies, by email or by phone.	

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes