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PATIENT INFORMATION LEAFLET AND INFORMED CONSENT

(Each patient must receive, read and understand this document before the start of the study)

TRIAL TITLE : Clinical Trial Number CSTI571 0114

An Expanded Access Protocol of STI571 in Adult Patients with Chronic Myeloid Leukemia in Accelerated phase or Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

INTRODUCTION

You have been asked if you would be willing to take part in this research study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study, and sign the consent form, you should fully understand what is involved. If you have any questions which are not fully explained in this leaflet, do not hesitate to ask the Study Doctor. You should not agree to take part unless you are completely happy about all the procedures involved. In the best interest of your health it is recommended that you discuss with or inform your personal doctor of your possible participation in this study, wherever possible.

PURPOSE OF THE STUDY

This study is part of an expanded access program which will be conducted in 21 countries world-wide. The purpose of this study is to further evaluate safety and to provide patients with access to this new drug. . The study will stop as soon as the drug, STI571, becomes commercially available at which time drug administration per protocol will stop and you will continue therapy via prescription from your personal doctor.

You have been invited to participate in this study because you have either Chronic Myeloid Leukemia (CML) in accelerated phase or Acute Lymphoblastic Leukemia (ALL). CML is characterized by an abnormal chromosome called the "Philadelphia chromosome" which is also present in approximately 20% of adult patients with ALL. The Philadelphia chromosome creates an abnormal enzyme that causes leukemia cells to grow. An experimental agent, called STI571, has been developed to stop the enzyme that causes leukemia cells to grow. In a preliminary study with STI571 in patients with either CML in accelerated phase or with ALL and at the dose of STI571 that will be used in this study, approximately three quarters (75%) of patients had white blood cell counts that returned to normal. However, it is too soon to tell if these benefits will persist. The purpose of this study is to further test the side effects and anti-leukemic benefits of STI571 in patients with CML in accelerated phase.

NUMBER OF PATIENTS

If you decide to take part, you will be one of approximately 1200 patients world-wide, recruited from 21 countries.
Approximately 30 patients in total are expected from South Africa.

DURATION OF THE STUDY

The study will stop as soon as the drug, STI571, becomes commercially available (expected to be mid-2002) at which time drug administration per protocol will stop and you will continue therapy via prescription from your personal doctor.

PROCEDURES

Before receiving the study drug, you will undergo a series of tests to evaluate your disease. These include a physical examination, measuring your blood pressure, pulse rate, and temperature, obtaining your weight, and approximately 1-2 teaspoons of blood will be collected for routine tests. Within 28 days prior to starting the study drug, a sample of your bone marrow will be required to assess the status of your disease. A bone marrow is a procedure in which an area of the hip is numbed and a small amount of bone marrow aspiration is withdrawn through a needle. This procedure may be uncomfortable and you should ask your study doctor to describe the procedure in detail to you if you are not familiar with it. You will also be asked about any other medical conditions that you may have and about other medication you are taking.

If these tests confirm that you can enter the study, and you agree to participate, you will be given 600 mg of the experimental drug STI571 by mouth in capsule form, once daily for up to 12 months. If you do not respond to treatment by demonstrating a reduction and stabilization in your white blood cell count and platelet count after 3 months of treatment, or do not demonstrate a major cytogenetic response (decrease in the number of Philadelphia chromosome positive cells in your bone marrow) after 12 months of treatment with the study drug at a dose of 600 mg/day, your study doctor may suggest an increase in the dose to 400 mg twice a day (for a total daily dose of 800 mg/day)

STI571 should be taken each morning together with breakfast, in a sitting position, with a large glass of water. If you are taking STI571 twice daily, the second dose should be taken together with the evening meal. The drug is taken in a sitting position because STI is a local irritant, and if taken in a sitting position, this assures that the drug does not get stuck in the oesophagus.

You must not eat grapefruit or drink grapefruit juice while taking STI57, as grapefruit is a very powerful inhibitor of cytochrome 3A4 which is responsible for the metabolism of STI. The nett result could be greatly increased plasma levels of STI.

Bottles containing the capsules will be given to you periodically. You must return any unused supplies and the completed patient diary with each visit to the study centre.

After completing 12 months of therapy, your study doctor will discuss with you further treatment possibilities. You may be eligible to receive further therapy as long as tests show that your disease is not worsening and you have experienced no major side effects, or you may receive other kinds of treatment for your illness.

The protocol requires that the first visit is at the study centre and that you return to the study centre every 6 months for bone marrow assessments and cytogenetic studies (determining the number of Philadelphia chromosome positive cells) while you are receiving study drug. All other visits may be at the study centre or you may return to your personal doctor.

The schedule of evaluations required by the protocol must be adhered to, whether you return to the study centre for each evaluation, or to your personal doctor. If you return to your personal doctor, the results of each required evaluation must be forwarded to your Study Doctor by fax.

Routine blood tests for blood counts and chemistries will be collected weekly for the first 4 weeks then every two weeks until discontinuing study drug. If your liver function tests or blood counts become abnormal, weekly or twice weekly blood tests may be required. These tests are performed to monitor the safety of the drug.

At the visits to the study centre or your personal doctor, a physical examination and monitoring of your blood pressure, pulse, and temperature will be recorded every month until discontinuing study drug.

If you stop the study drug before 12 months, the following evaluations will be performed to evaluate your disease: a physical examination, vital signs, bone marrow sample, and routine blood tests. You will be discontinued from the study if your disease progresses, or if there are any safety concerns.

You will be asked about any symptoms you may experience and all other medications you are taking while you are participating in this study. Before you take any other medications you should discuss this with your Study Doctor.

CAN ANY OF THESE TRIAL PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

Venipunctures (i.e. drawing blood), and bone marrow analysis are normally done as part of routine medical care and present a slight risk of discomfort.

Approximately 1-2 teaspoons of blood will be collected at each visit for routine tests. Routine blood tests include haematology (blood cells), liver function tests, and other biochemistriey tests. During the collection of blood samples, you may experience pain and/or bruising at the site where the blood is drawn, or less commonly fainting or swelling of the vein, infection and bleeding.

A sample of your bone marrow will be required six monthly to assess the status of your disease. A bone marrow is a procedure in which an area of the hip is numbed and a small amount of bone marrow is withdrawn through a needle. This procedure may be uncomfortable and you should ask your doctor to describe the procedure in detail to you if you are not familiar with it.

The Study Doctor is aware of the side effects, as well as the best methods for treating them. Your protection is that the tests are performed under clean conditions by experienced personnel.

RISKS

Approximately 1600 patients with CML in chronic phase and approximately 1058 patients in accelerated phase have been treated with STI571 since June 1998. STI571 has been generally well tolerated. The most commonly reported side effects related to taking STI571 were mild/moderate muscle cramps in the feet and legs; indigestion, nausea, and headache. Laboratory abnormalities observed in some patients who required temporarily interrupting study drug or reducing the dose, included elevated liver or renal function tests and low platelet or white blood cell counts.

As a consequence of an abnormal renal function test, some patients have reported a rapid gain in body weight. Therefore, you are invited to closely monitor your body weight twice a week and report to your doctor any rapid increase greater than 2 kg. If this happens, a check-up including physical examination, blood tests and X-rays will be performed as required by your condition.

Lowering of your white blood cell count could lead to an increased risk of infection and lowering of your platelet count could lead to an increased risk of bleeding. If you should develop a fever when your white blood count is low, you may need to be hospitalized to receive treatment. Transfusions may be required to counteract the effects of a low platelet count. Your blood counts will be monitored closely and the dose of your medication will be adjusted if your blood counts are low. It is expected that any lowering of your blood cells will be reversed by decreasing the dose of the drug, or by temporarily stopping the study drug. However, if your blood cells do not recover, death eventually would occur.

1- Panadol

Myprodol ?

One patient taking STI571 who had no known history of liver problems has died on study due to liver failure. The patient was also taking acetaminophen (Tylenol®), also known as paracetamol. It is recommended to adhere carefully to the instructions and warnings included in the acetaminophen or paracetamol package. Additionally, it is recommended that you carefully review all other over-the-counter medications that you are taking, since these may sometimes contain acetaminophen or paracetamol in combination with other drugs.

One patient with a history of heart problems experienced chest pain while on study drug and two patients had gastrointestinal bleeding episodes while on study.

Other side effects may occur and could be severe or life-threatening. You will be closely monitored for any side effects and should report any changes in the way you feel to your study doctor. You will be kept fully informed of any events that occur during the course of the trial, which might affect your safety.

As with many cancer treatments, it is important that you do not become pregnant or father a child until your treatment has completely finished. This is because the drug can affect the development of the baby in the womb. The risks to an unborn human fetus or a nursing child from this study drug are not known.

Women who are pregnant or nursing a child may NOT participate in this trial. If you are a female of childbearing potential, your study doctor must confirm that you are not pregnant by drawing a sample of blood at the screening visit. You must confirm that you do not intend to become pregnant during the trial. If you are of childbearing potential your study doctor will discuss appropriate birth control measures with you. If you suspect that you have become pregnant during the clinical trial (miss an expected menstrual period), contact your study doctor immediately. If you are pregnant you will be withdrawn from the study.

You should use a barrier method of contraception during the trial. For men and women this should continue for at least three months after the last dose of drug to ensure that the drug has cleared from the body.

As with any investigational drug, the use of the trial drugs may be associated with certain unforeseeable risks. You are expected to report all side effects promptly to the Study Doctor, should they occur. The Study Doctor is prepared to handle any medical problem should it be necessary.

BENEFITS

There is no guaranteed medical benefit by participating in this study. However, by serving as a subject, you may contribute new information, which may benefit patients in the future.

ALTERNATIVE TREATMENTS

You DO NOT have to take part in this study if you do not want to. Other treatments available for CML and ALL include bone marrow transplantation and treatment with hydroxyurea or other chemotherapy. Anticipated responses on other chemotherapeutic agents include decreased blood cells, alopecia (loss of hair), gastrointestinal side effects like diarrhoea, nausea, and vomiting, lethargy and weight loss. Please discuss alternative treatments with your Study Doctor. You may decide to have no further treatment and receive supportive care only. If you decide to take part you may withdraw at any time without having to give a reason. Your decision not to take part will not affect your care and management in any way.

CONFIDENTIALITY

All information obtained during the course of this trial is strictly confidential. Data that may be reported in scientific journals will not include any information which identifies you as a patient in this trial.
In connection with this trial, it might be important for domestic and foreign regulatory health authorities and the Ethics Committee, as well as your personal doctor, to be able to review your medical records pertaining to this trial. Therefore, you hereby authorise your Study Doctor to release your medical records to **Novartis South Africa (Pty) Ltd**, its employees or agents, domestic and foreign regulatory health authorities and the South African Medical Association Research Ethics Committee. You understand that these records will be utilised by them only in connection with carrying out their obligations relating to this clinical trial.

Any information uncovered regarding your test results or state of health as a result of your participation in this trial will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this trial but this information will not be disclosed to any third party in addition to the ones mentioned above, without your written permission The only exception to this rule will be cases in which a law exists compelling us to report individuals infected with communicable diseases. In this case, you will be informed of our intent to disclose such information to the authorised state agency

ETHICAL APPROVAL

This clinical trial Protocol was submitted to the Research Ethics Committee of the South African Medical Association and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki, (last updated October 1996), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy of the Declaration of Helsinki may be obtained from your Study Doctor should you wish to review it.

EARLY TERMINATION/STUDY TERMINATION

Your Study Doctor can stop your participation in this trial at any time without your consent if it appears harmful to you, if you fail to follow instructions for participation in the study, if you become pregnant during the course of the study, if it is discovered at a later time that you did not meet the study requirements, or if the study is cancelled by the sponsor.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

Your participation in this trial is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to other medical care.

COMPENSATION/ INSURANCE

As this is an expanded access program, the purpose of which is to makeSTI571 available to a larger number of patients than could otherwise be treated in formal registration trials, Novartis will not provide payment for trial procedures, all of which are standard care in the normal course of the disease. No special study related procedures will be performed.

Novartis has obtained insurance for you and the Study Doctor in the event of trial related injury. Novartis will abide by the Association of the British Pharmaceutical Industry Clinical Trial Compensation Guidelines – a copy of which may be obtained from your Study Doctor should you wish to review it.

Novartis will provide payment for reasonable, unreimbursed medical expenses, including hospitalization, which you may incur as a direct result of STI571 or its administration in accordance with the Protocol, as determined by Novartis and the Study Doctor. Novartis will not provide payment for expenses that are in any way attributable to the negligence or misconduct of any person employed by or acting on behalf of the Institution or your failure to follow instructions. Novartis will not pay for medical expenses for injuries

unrelated to STI571, or which are in any way attributable to the natural course of any underlying disease or treatment process. No other type of compensation will be provided by Novartis.

You must notify the Study Doctor immediately of any research-related injury and the nature of the expenses to be covered. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact your Study Doctor.

By signing this form you have not given up any of the legal rights which you otherwise would have as a participant in a research study.

You will not be paid to participate in this trial.

Please note that if you have a life insurance policy, you should notify the appropriate insurance company concerned of your intention to participate in a clinical trial.

SOURCE OF ADDITIONAL INFORMATION

You can keep a copy of this document.

If you need more information on this study please contact:

PROF. P. JACOBS during office hours on: 021-7992569

or after office hours by telephoning: 021-7992555/9

SR. LORNA THOMSON WK 7992650

082-5347501

INFORMED CONSENT

I hereby confirm that I have been informed by the Study Doctor

Prof P. Jacobs
Study Doctor's/Co-Study Doctors name

about the nature, conduct, benefits and risks of clinical trial CSTI571 0114. I have also received, read and understand the written information (Patient Information and Informed Consent Form) regarding the clinical trial.

I am aware that the results of the trial, including personal details regarding my age, sex, date of birth, initials and diagnosis will be anonymously processed into a trial report.

I may, at any stage, without prejudice, withdraw my consent and participation in the trial.

I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the trial.

Patient's Name: (PRINT) M J MAARTENS

Patient's Signature

Date: (DATED BY THE PATIENT) 20/11/2001

Patient's name, signature and date all to be inserted by the patient on the same day this form is signed.

Witness's Name: (PRINT) J.J. Maartens

Witness's Signature

Date: (DATED BY THE WITNESS) 20/11/2001

Witness's name, signature and date all to be inserted by the witness on the same day this form is signed.

I, the supervising Study Doctor confirm that I have fully explained the nature, purpose and reasonably foreseeable risks of participating in the trial to the patient and that he/she has read and kept a copy of the Patient Information Leaflet and Informed Consent Form. He/she has freely agreed to participate in the trial.

Study Doctor's Name: (PRINT) PETER JACOBS

Study Doctor's Signature

Date: (DATED BY THE STUDY DOCTOR) 20.11.2001

Study Doctor's name, signature and date all to be inserted by the Study Doctor on the same day this form is signed.

Patient's Assigned Study Number:	
Patient's Initials:	