SINGLE PATIENT INVESTIGATIONAL NEW DRUG (IND) APPLICATION CONSENT FORM

This form describes the potential risks of TMC125 as part of a regimen including TMC114/RTV and an investigator-selected OBR regimen in anHIV-1 infected subject with limited treatment options.

CONTACT DETAILS PROGRAM DOCTOR

Name:.....

Address:.....

Telephone number:.....

ADDITIONAL CONTACT DETAILS (IF APPLICABLE)

Name:.....

Address:.....

Telephone number:.....

INTRODUCTION

You have been asked to participate in a TMC125 Single Patient IND (Investigational New Drug) access program with two new investigational drugs called and TMC114. These drugs are being developed by Tibotec Pharmaceuticals Ltd., Little Island; CO Cork in Ireland. However, before you agree to take part in this single patient access program, please read this consent form carefully and ask as many questions as you need in order to be sure you understand the program procedures, including possible risks and benefits. TMC 114 will be provided via a current expanded access program. TMC 125 will be provided via a separate program called Single Patient IND.

This consent form contains important information to help you to decide whether or not it is in your best interest to participate in this program. If you have questions that are not properly explained or answered in this consent form, someone of the research staff will be available to give you more information.

PART I: PROGRAM SPECIFIC INFORMATION

INVESTIGATIONAL MEDICATIONS

 and TMC114 are in process of development for the treatment of patients who are infected with the Human Immunodeficiency Virus (HIV). Neither drug is approved for use by the US Food and Drug Administration (FDA) or other Regulatory Authorities in the European Economic Area (EEA). Therefore, they can only be used in this research program.

TMC125 is from a class of drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Other drugs in this class include Sustiva® and Viramune®. These drugs help to slow or stop the growth of HIV. TMC125 may be effective for you even if other drugs in this class (like Sustiva® or Viramune®) don't work for you.
The drug TMC114 belongs to the group or class of drugs known as protease inhibitors (PIs). In two programs currently enrolling called DUET 1 and DUET 2, TMC114 will be given with a low dose of ritonavir (RTV, a PI commonly used with other PIs) plus TMC 125 plus optimized background therapy (OBT), compared to TMC 114+ TMC 125 placebo + OBT. You will be getting direct access of these two medications without having to enroll in those studies because you have no active OBT that can ensure that you can control your viral load successfully.

DESCRIPTION AND PURPOSE OF THE PROGRAM

When you enroll in the program you will receive TMC114 along with low dose ritonavir together with at least 2 other anti-HIV treatments. These additional treatments are called the "Optimized Background Regimen" (OBR).

Selection of the OBR will be done by your doctor and is based on the results of your personal HIV drug resistance test, your previous HIV treatment history and other factors specific to your situation.

TMC125 200 mg and TMC114/RTV 600/100 mg will be given twice daily. The OBR will consist of at least 2 drugs from the anti-HIV treatment class known as nucleoside reverse transcriptase inhibitor (s) (NRTI[s]) with or without enfuvirtide (T-20).

PROGRAM PROCEDURES

Decision to participate

Before you decide to participate in this program,, you will receive a full explanation about the risks and potential benefits, both orally and in writing (this is the document you are now reading). If you want to participate in this program, you must first confirm in writing that you agree to participate.

Treatment period

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After determining the OBR and discussing your new treatments with your doctor, your new treatment will consist of:

200 mg TMC125 (2 tablets twice daily)

IN COMBINATION WITH

600 mg TMC114/100 mg ritonavir (2 TMC114 tablets and 1 ritonavir capsule twice daily)

AND

Optimized Background Regimen (OBR) consisting of NRTI(s) (nucleoside reverse transcriptase inhibitors) with or without T-20 (Enfuvirtide)

It is possible that you or your program doctor will decide to end your participation earlier (see section “Participation and Termination”).

Follow-up period

This period lasts until TMC 125 is available via expanded access program. TMC 114 may be approved for commercial distribution in the next few months also. You will be responsible for obtaining these two medicines after this program ends.

Unscheduled visits

During the course of the program, you may be asked to return to the program clinic for an unscheduled visit. During that visit the program doctor may want to do some additional testing of any abnormal laboratory value observed in your blood or urine samples or to follow-up on a specific side effect or adverse event you may experience. Blood (approximately 25 ml or 5 teaspoons) may be drawn.

EXPLANATION OF EXAMINATIONS

Physical Examination

A full examination of all body parts will be done.

Urine Collection and Blood Sampling

- Urine and blood samples will be collected for routine safety testing, which includes testing of your immune function, HIV resistance, and the amount of HIV virus present in your blood. You need to fast for at least 10 hours before the routine blood tests.

- In case you have additional program visits, small additional amounts of blood may be drawn (a maximum of 25 ml or 5 teaspoons).

Vital signs

Your pulse and blood pressure will be measured.

Body Measurements

Your height and weight will be measured.

RISKS AND BENEFITS

Each of the program medications can have undesirable effects. Your program doctor can inform you of the potential risks or discomforts associated with your individually optimized anti-HIV therapy. At any time during the program, you have the right to ask questions on possible and/or known risks.

By participating in this program, the progress of your condition will be closely monitored. It is possible *that by participating in this program your condition may improve, and* that this program may be helpful in developing a new therapy *for others with similar illnesses*.

TMC125

Available animal data show that TMC125 may cause liver, kidney, thyroid and skin effects and changes in blood clotting parameters. Therefore, your health will be monitored closely during the program.
Recent data have demonstrated that male mice treated with TMC125 suffered from internal bleeding in heart and several other organs, which likely caused death in some animals at higher doses. These findings have not been seen in female mice, or in rats or dogs. The relevance of these findings for human subjects is probably low, because it appears to be species-specific. In studies in healthy volunteers and HIV-1 infected subjects, there is no evidence of clinically relevant changes similar or related to the findings in male mice.

As of September 2004, 216 healthy volunteers have received TMC125 for at least 7 days. In these programs, the most frequently reported adverse events were headache (34%), rash (14%), flatulence (gas) (13%) diarrhea (12%), itchiness (11%), sleepiness (10%), and abdominal pain (10%). Most of these adverse events were mild or moderate in severity.

Four healthy volunteers (1.3 %) developed rash with mouth ulcers (sores) or vesicles (blister-like). These types of rashes were seen after a single dose of TMC125. In the multiple dose programs in healthy volunteers, there were no reports of rash with blisters. Rashes with mouth ulcers or blisters can be life threatening and need immediate medical attention. It is important that you inform your program doctor immediately and make an appointment to come to the clinic for a detailed evaluation, if you develop any skin changes including rash with any one of these signs: fever, nausea, vomiting, diarrhea, abdominal pain, extreme tiredness, aches, generally ill feelings, sore throat, shortness of breath or cough.

A healthy volunteer who received a single dose of 400 mg TMC125 was found dead three days later. The cause of death of this volunteer is unknown, possibly heart related. The program doctor did not think the death was related to TMC125.
In the healthy volunteer programs, there were no significant changes in vital signs (pulse, breathing rate and blood pressure), heart rhythm or laboratory test results.
In patient studies, through December 2004, the following medically important adverse events had been reported.
One patient suffered from a decrease in all blood cells (red, white and platelets) and was hospitalized after being treated for his HIV-infection with TMC125 or placebo and several other drugs. An overall decrease in blood cells as seen in this patient, can be potentially life threatening.

Four HIV-1 infected patients reported pancreatitis (an inflammation of the pancreas gland) and were hospitalized for that condition.
An HIV infected patient died in January 2005 while participating in a long-term program with TMC125. This patient had been treated for over 4 months with TMC125 in combination with other anti-HIV drugs. He became ill over a period of 48 hours and went to hospital with difficulty breathing. The immediate cause of death was probably a heart attack; but the disease or disorder leading to this heart attack is not clear. This cannot be confirmed, as an autopsy was not performed. Although this patient had risk factors for heart disease, it cannot be excluded that TMC125 contributed to this event.
Since TMC125 may cause dizziness, reduced concentration and/or drowsiness, you should not perform potentially dangerous tasks such as driving or operating machinery when experiencing these symptoms.

During the present program, your body functions will be monitored very closely to detect possible negative effects of the medication. It is very important that you tell your program doctor of any changes in your medical condition while taking part in this program.
Studies have been done with TMC125 in combination with a number of other drugs to look if TMC125 caused changes in blood levels of other drugs and vice versa. Your physician will provide you with information on these drug combinations that are relevant for you.
You have the right to ask any questions on the possible and/or known risks of this program at anytime.

TMC114
The most frequently observed side effects of TMC114 when given with low dose ritonavir were diarrhea, nausea and headache, mostly mild or moderate in severity. These side effects are commonly seen with other components of HIV therapy and can often be easily managed by your program doctor.
Skin rash has also been reported with TMC114, as seen with other HIV drugs. This potential side effect usually occurs within the first 2 weeks, is often mild or moderate in severity, typically resolves within one week and does not necessarily lead to treatment interruption. However, certain cases of moderate and all cases of severe skin rashes will require temporary or complete interruption of HIV medicine and additional program visits.
Chronic HIV therapy has been linked to changes in body shape (for example: fat distribution) and perception of body image. At present, no information on the potential effect of TMC114 on these body changes is known. Please refer to the program doctor if you feel you are experiencing any changes.
Different antiretroviral drugs may affect fat and sugar metabolism. The most frequently observed laboratory abnormalities with TMC114 given with a low dose of ritonavir, are increases in blood fats (triglycerides and cholesterol) and sugars (glucose). If you should experience such changes, your program doctor will evaluate your condition, tell you if modifications of your dietary habits and level of physical activity are needed, and whether medical intervention is warranted.
Liver and pancreatic laboratory abnormalities may also be observed when taking HIV therapy. Therefore, these and other organ functions will be monitored throughout the program. In the event abnormalities are detected, your program doctor will evaluate your condition and provide you with the necessary recommendations.
The knowledge of potential long-term impact of both HIV infection and antiretroviral therapy on the heart and blood vessels is still evolving. In addition, many previously recognized risk factors such as older age, smoking, excessive alcohol intake, recreational drug use, family history of heart disease, obesity, lipid disorders (increased blood fats), diabetes (increased blood sugars) and sedentary lifestyle also increase the risk of cardiovascular disease and complications. Providing your program doctor with the most complete medical history is the best way to determine if you can benefit from risk reduction measures.

Administration of TMC125 and TMC114 has led to skin rashes in some people. If you experience any skin problems or other symptoms, unscheduled program visits will most likely be performed to carefully assess and monitor your condition.

If your skin shows any unusual qualities during the program (mainly rash, but including unusual boils or blisters) you should inform the program doctor immediately and go to the program site for a prompt medical evaluation.

It is highly recommended that you see the program doctor as soon as your rash or skin condition appears. Depending on the severity of the skin rash, your HIV drug regimen may be interrupted and additional assessments and visits may be required.

Risk of Ritonavir

Ritonavir (Norvir®) is also a protease inhibitor. Ritonavir is used for the treatment of an infection with HIV. Ritonavir is often used to increase the concentration in blood of other anti-HIV drugs and not for the antiviral effect. The dosing in this program is 100 mg twice daily. TMC114 is used in combination with ritonavir because ritonavir increases the levels of TMC114 in the blood. Furthermore, less adverse events are observed when TMC114 is given in combination with ritonavir.

In general, ritonavir is well tolerated. Ritonavir could cause the following adverse events: nausea, vomitting, diarrhoea, gastric complaints, decreased appetite and stomachache. Other adverse events are: headache, tingling in arms and legs and the mouth area, tiredness, altered taste sensations, rash, difficulties in breathing, and dizziness. In the blood changes in the liver enzymes, cholesterol and triglycerides could occur.
More information about ritonavir is available at the program location. It is possible to obtain a copy of this information.

Blood Draw Risks

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body (1%). A small blood clot may form where the needle enters the body or there may be swelling in the area. Rarely, fainting or local infection may occur. Care will be taken to prevent these complications.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the program doctor or program staff right away if you have any problems. During the program, you will be informed about additional information that may affect whether or not you still wish to continue the program.

Reproductive Risks

No data are currently available with TMC125 or TMC114 concerning risks to embryo, fetus or nursing.

Women who can get pregnant or are breastfeeding

You may not take part in this program if you are breastfeeding, are pregnant, think that you may be pregnant, or are trying to get pregnant. If you are pregnant or breastfeeding, there may be risks to you and your baby that are not known at this time. Women who can get pregnant will be tested for pregnancy during the program.
You must avoid getting pregnant in order to take part in this research program. You should not have heterosexual intercourse or you should use a method of birth control that is acceptable to you, the program doctor, and the sponsor. Women of childbearing potential should use an adequate method of birth control, such as female condom with spermicide, intrauterine device in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap with spermicide), be non-heterosexually active, practice heterosexual abstinence, or have a vasectomized partner.
It is important for you to tell the program doctor at once if you get pregnant or think that you might be pregnant while you are in the research program. If this happens, the program doctor will discuss with you what you should do. Since there might be risks for an unborn child, which are currently unforeseen, you will be asked to stop taking part in the program if you get pregnant. You may also be asked questions about your pregnancy and the baby.

Male subjects

It is advised that you use a condom to reduce the risk of transmission of HIV when having sexual intercourse. Since the effects of a new drug on conception are unknown, it is important that you follow adequate birth control methods if you have not been surgically sterilized (minimally one month prior to screening) and are having heterosexual intercourse from screening onwards until one month after the last program drug administration.
These methods include using a condom with spermicide, a condom combined with either hormonal contraceptives, a coil, diaphragm, cervical cap or female condom or practicing heterosexual abstinence. These restrictions are not applicable if your female sexual partner has had a tubal ligation, a total hysterectomy (surgery of removal of the womb) or if she is postmenopausal for at least two years. You should inform your doctor if your partner becomes pregnant during the program or within one month after the last program drug administration.

Rash

If you develop a rash or have itching during treatment, you should inform your program doctor immediately and make an appointment to come to the clinic for a detailed evaluation. It is recommended that you see your program doctor the day your rash appears. If you do get a rash,

it needs to be watched closely by your doctor and you may be asked to regularly see a dermatologist (skin doctor).

ALTERNATIVE TREATMENTS AND ADDITIONAL INFORMATION

Alternative treatments for your illness are available. In case you have any questions, please see your doctor.

You have the right to ask any questions concerning the potential and/or known hazards of this program at any time. Should you as a result of the participation in this program, be harmed in any way, you will receive appropriate medical treatment.

If additional information becomes available during the program that might affect your willingness to continue in this program, you or your legally acceptable representative will be informed in a timely manner.

YOUR ROLE IN THE PROGRAM

Your responsibilities as a program subject include the following:

- provide truthful information about your medical history and current conditions
- tell the program doctor about any problems you have during the program
- do not take any other drugs or remedies (either prescription, over the counter, or herbal remedies) unless the program doctor has approved them
- tell the program doctor of any new medicine or drug you take during the program
- return all empty, partially used, and unused program drug materials and packaging at each visit
- inform the program doctor if you experience any problems while taking program drug, particularly any skin rashes

PROGRAM RELATED INJURY

In compliance with the applicable laws, the sponsor has provided for medical treatment and/or compensation in the event of damage and/or a lesion resulting from participation in the clinical program.

In case of program related injury or in case you need additional information concerning the program and your rights and obligations as a clinical program subject, you should contact *specify name, address and telephone of the investigator and/or contact person according local regulations,* at any time.

You have the right to ask any questions concerning the potential and/or known hazards of this program at any time. Should you as a result of the participation in this program, be harmed in any way, you will receive appropriate medical treatment.

If additional information becomes available during the program that might affect your willingness to continue in this program, you or your legally acceptable representative will be informed in a timely manner.

COSTS

The sponsor will provide you with the investigational drug free of charge. The sponsor, however, will not provide nor pay for the background medicine selected by the program doctor. Your current third party payer will have to cover costs related to medical blood tests and doctor’s visits.

REMUNERATION

You will not receive any form of payment for your participation in this program.

Your physician does not receive any compensation for filling up all the required forms for you to get access to these investigational compounds

PART II: GENERAL INFORMATION

PARTICIPATION AND TERMINATION

Your decision to participate in this program is voluntary. You may refuse to participate or you can withdraw from the program at any time. Your refusal to participate or wish to withdraw before completion of the program period will not in any way effect or influence current or potential future medical care.

Your participation in this program may be terminated if your doctor decides that it is in your best interest to stop or if the sponsor decides to stop the conduct of the program. Early withdrawal can also occur in case the procedures described in this document are not properly followed or in case forbidden medication was taken.

If you leave the program prematurely, you are asked to come in for a final evaluation. During that visit you will be asked about any non-desirable effects you may have encountered during the program*. It is important that at each visit and certainly at the termination visit you return the remainder of the medication, the empty containers and your diary.*

CONFIDENTIALITY

Representatives of the sponsor (monitors and auditors), the *Independent Ethics Committee (IEC) /Institutional Review Board (IRB)* and/or Regulatory Authorities will be granted direct access to your original medical records for verification of clinical program procedures and/or data, without violating your confidentiality according to the laws and regulations applicable in your country. By signing this informed consent form you are authorizing such access.

All records that identify you will be kept confidential and will not be made publicly available. If the results of the program are published, your identity will remain confidential. If reference to you is made, this will only be done by using code numbers.

The information gathered during this program will be processed electronically by the sponsor of this program. By signing the attached informed consent form, you are authorizing such processing of data. You will be entitled to request confirmation of the existence of personal data held by the sponsor and will have the right to rectify erroneous or inaccurate data.

Your personal data generated during this program may be passed on to the appropriate authorities, to the sponsor / manufacturer of the medicinal product under investigation and to people or companies working on behalf of the sponsor / manufacturer. The information may also be communicated to other countries of the European Economic Area (EEA) and to the USA. Some of the non-EEA countries to which the data may be transferred may offer varying levels of personal data protection. However, information that directly identifies you, such as your name and address, will not be transmitted. The sponsor may use the collected information to determine if the program drug is safe and effective, to compare the program drug to other drugs, for regulatory activities and for future research activities that are unanticipated at this time.

All personal data will be entered anonymously and your identity will not be revealed.

This permission to share your personal health information for this program does not have an expiration date. If you no longer want to share your personal health information, you may cancel your permission at any time by writing to the program staff and/or the program doctor at the address below:

Insert address

If you cancel your permission after you have started in the program, the program staff and the program doctor will stop collecting your personal health information. Although they will stop collecting new information about you, they will need to use the information they have already collected to evaluate the program results. If you start the program and then cancel your permission, you will not be able to continue to participate in the program. This is because the program staff and/or the program doctor would not be able to collect the information needed to evaluate the program drug.

SUBJECT'S INFORMED CONSENT

TMC 125
Single Patient
IND

I, _____ (name in printing) have read and understood the attached Subject Information Sheet and I agree to take part in this program of single patient IND access of

I was given a copy of this signed and dated Informed Consent Form and the corresponding Subject Information Sheet. I have received an explanation of the nature, purpose, duration and foreseeable effects of this program and of what I will be expected to do. The possible risks and benefits of this program *and the alternative treatments available for my illness* have been explained to me. I was given enough time and opportunity to inquire about the program and all my questions were answered to my satisfaction.

I agree to fully co-operate with the supervising doctor and will tell him if I suffer any unexpected or unusual symptoms. I confirm that I have informed the supervising doctor of any medication/drug, of whatever nature, I have taken in the month preceding the start of the program, or I am taking or plan to take, whether prescribed or not.☐

I have been informed that, in compliance with the applicable laws, the sponsor has provided for medical treatment and/or compensation in the event of damage and/or lesion resulting from participation in the clinical program.

I am aware that this program has been reviewed and approved by an *Independent Ethics Committee/Institutional Review Board (IEC/IRB).*

I am free to withdraw from the program at any time, without the need to justify my decision *and without any disadvantage to my potential medical treatment*.

I agree that results of this program may be passed on to the appropriate authorities and to the sponsor of the drug under investigation. My name and address will be kept secret.

I understand that representatives of the Sponsor, the *IEC/IRB* or Regulatory Authorities may wish to inspect my medical records to verify the information collected. By signing this document I give permission for this review of my records.

I understand that no new data will be added to the database in the event of withdrawal of consent and that I may require to destroy all previously retained identifiable samples.

I am aware that the investigator might have to ask for new consent in case of additional analyses (other then specified in part II) on retained identified samples and that I have the right to refuse.

I understand that I have the right to access and to correct my personal data if needed.

I understand the need and I agree with electronic processing and transfer of the data obtained during this clinical program.

I voluntarily consent to participate in this program.

_____

Subject's Signature *Date (DD/MMM/YYYY)*

I confirm that I have explained the nature, purpose and foreseeable effects of the program to the subject whose name is printed above. The subject consented to participate by his/her personally dated signature.

_____

Informed Consent Provider's Signature *Date (DD/MMM/YYYY)*

_____

Informed Consent Provider's Name in printing

SUBJECT'S INFORMED CONSENT (BY LEGALLY ACCEPTABLE REPRESENTATIVE) **SINGLE PATIENT IND**

I, _____ (name of the legally acceptable representative in printing) have read and understood the attached Subject Information Sheet and I agree to the participation of the following subject: _____ (name of the subject in printing) in this program of Single Patient IND access of

I was given a copy of this signed and dated Informed Consent Form and the corresponding Subject Information Sheet. The subject and myself received an explanation of the nature, purpose, duration and foreseeable effects of this program and of what the subject will be expected to do. The possible risks and benefits of this program *and the alternative treatments available for the subject's illness* have been explained. The subject and myself were given enough time and opportunity to inquire about this program and all questions were answered to our satisfaction.

I agree to fully co-operate with the supervising doctor and will tell him if the subject suffers any unexpected or unusual symptoms. I confirm that I have informed the supervising doctor of any medication/drug, of whatever nature, the subject has taken in the month preceding the start of the program, or is taking or plans to take, whether prescribed or not.

☐

We have been informed that, in compliance with the applicable laws, the sponsor has provided for medical treatment and/or compensation in the event of damage and/or lesion resulting from participation in the clinical program.

I am aware that this program has been reviewed and approved by an *Independent Ethics Committee (IEC) / Institutional Review Board (IRB).*

I understand that the subject is free to withdraw from the program at any time, without the need to justify this decision *and without any disadvantage to the potential medical treatment.*

I agree that results of the program may be passed on to the appropriate authorities and to the sponsor of the drug under investigation. The subject's name and address will be kept secret.

I understand that representatives of the Sponsor*, IEC/IRB* or Regulatory Authorities may wish to inspect the subject's medical records to verify the information collected. By signing this document I give permission for this review of the subject's medical records.

I understand that no new data will be added to the database in the event of withdrawal of consent and that the subject may require to destroy all previously retained identifiable samples.

I am aware that the investigator might have to ask for a new consent in case of additional analyses (other then specified in part II) on retained identified samples and that the subject has the right to refuse.

I understand that the subject has the right to access and to correct his/her personal data if needed.

I understand the need and I agree with electronic processing and transfer of the data obtained during this clinical program.

I agree to the subject's participation in this program.

_____

Legally Acceptable Representative's Signature *Date (DD/MMM/YYYY)*

_____

Legally Acceptable Representative's name in printing

_____

Legally Acceptable Representative's relation to the subject

I confirm that I have explained the nature, purpose and foreseeable effects of the program to the subject's Legally Acceptable Representative whose name is printed above, and that he/she agreed on the subject's participation in this program. The Legally Acceptable Representative confirmed the subject's participation in this program by the above dated signature.

_____

Informed Consent Provider's Signature *Date (DD/MMM/YYYY)*

_____

Informed Consent Provider's Name in printing