Royal Free Hampstead NHS
NHS Trust

Royal Free Hospital
Pond Street
London NW3 2QG

Subject initials_____

1. Study title

The MaxCmin2 Trial

A phase IV randomised, open-label, multicentre trial to evaluate the safety and efficacy of lopinavir/ritonavir (400/100 mg bid) versus saquinavir/ritonavir (1000/100 mg bid) in adult HIV-1 infected patients.

Final Protocol, version 1.1: 15th of February 2001

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide 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. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.
Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

3. What is the purpose of the study?

The purpose of this study is to determine which of two protease inhibitor combinations of drugs is best at lowering the amount of the HIV in your body and maintaining levels suppressed below the limit which the tests can currently measure. In addition the safety and tolerability of the combinations will be compared.

This study compares the use of either lopinavir with ritonavir or saquinavir soft gel with ritonavir in combination with other anti-HIV drugs. The current standard of care uses 3 drugs from 2 classes of medications. The advantage of the study regimen containing ritonavir as an additional drug with either of the two protease inhibitors is that this drug in small doses raises the blood levels of both lopinavir and saquinavir soft gel. This allows a twice daily rather than a three times daily regimen to be used which should make them easier to take.

The main purposes of the trial are:

- to look at the differences in viral load between those on lopinavir/ritonavir versus saquinavir/ritonavir
- to look at the effect on immune status in the two treatment groups by measuring CD4 count
- to learn more about resistance development during treatment
- to learn more about the safety and tolerance of the two treatments

4. Why have I been chosen?

You are being asked to participate in this study because you are HIV positive and you are deemed to possibly benefit from a switch in combination therapy because if side effects you are

Copy made on: 29/07/2020

WITN0644122_0001

Subject initials_____

experiencing or that you have failed to maintain virus suppression on you current regimen. Approximately 300 subjects world-wide will be in the study.

5. Do I have to take part?

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 your participation in this study stops for any reason, you will be asked to have the laboratory tests and physical examinations that are specified in the protocol for early termination.

6. What will happen to me if I take part?

If you wish to participate in this study it will be discussed with you and blood tests taken to determine your suitability for participation ("screening tests"). If you are eligible to participate in the study you will be asked to meet again (Day 1 in study). At Day 1 you will be asked to give details of your medical history and have some more blood tests taken.

Participants in the study will be randomised equally (like tossing a coin) to receive either

- lopinavir + ritonavir (800 mg + 100 mg twice daily)

  or
- saquinavir + ritonavir (1000 mg + 100 mg twice daily)

The randomised treatment will be given in combination with at least two other anti-HIV drugs. Which other drugs you will receive in combination with the randomised treatment is entirely up to you and your doctor to decide. The only restriction is that a protease inhibitor can not be included. There is a 1 in 2 chance that you will receive each regimen. This is an open study and both physician and patient will know what they are receiving. All three drugs are to be taken two times a day with food and water.

You will remain on the chosen combination for the duration of the trial unless side effects occur or you show sign of reduced effect of the study treatment.

Samples during study: You will be seen for screening and Day 1 as described above 1, and at Weeks 4, 12, 24, 36 and 48 in the study. Blood samples for safety analyses, viral measures and lymphocyte subsets will be taken at each visit and you will be examined.

Approximately 30-40 ml (3-4 tablespoons) of blood will be taken at each draw (total approximately 250 ml)

At each visit, you will be asked about any medications you might have taken since the last visit and any illness that might have occurred since the last visit. Any changes in your medication and/or your health will be recorded.

You will be asked to return to the clinic, at the end of the study, for a follow up visit. At this visit, you will have a complete physical examination, including vital signs, urine and blood tests for safety, blood tests to see the activity level of your HIV virus and to check on your immune system. You will be asked about any medications you might have taken since the last visit a

Copy made on: 29/07/2020

Subject initials_____

any illness that might have occurred since the last visit. Any changes in your medications and/or your health will be recorded.

The study takes 48 weeks and includes approximately 6 visits to the doctor and nurses who are conducting this research.

7. What do I have to do?

While you are participating in this study you should not use any medications (over-the-counter, prescription, or illegal) without approval from the study doctor.

8. What is the drug or procedure being tested?

Lopinavir, saquinavir soft gel and ritonavir are all licensed medications for HIV disease. They are all protease inhibitors and have shown potent activity against HIV. The Lopinavir will taken as [redacted] 400mg capsules twice daily, the saquinavir soft gel will be given as five 200mg capsules twice daily and both drugs will be taken concurrently with ritonavir 100mg twice daily.

GRO-C

9. What are the alternatives for diagnosis or treatment?

Alternative treatments or procedures are available for the treatment of HIV, including approved and investigational drugs. Your doctor will discuss the benefits and disadvantages of alternative treatments for HIV with you.
If you end participation in the study or if study treatment is discontinued, your study doctor may recommend an alternative treatment for you. The study sponsor does not pay for alternative treatments.

10. What are the side effects of taking part?

Using a needle and syringe to remove blood from the vein is called "a blood draw". It may be necessary to insert a needle into your vein more than once if blood does not come out the first time. At each scheduled blood draw, a new needle will be used. During blood draws you may have pain and/or bruising at the place on your arm where blood is taken. Blood clots can form and infections may occur, but these very rarely occur. If you feel faint during or after a blood draw, you should lie down right away to avoid falling down, then you should notify one of the study staff.

As one reason for this study is to learn more about the possible side effects of the combinations of study drugs, it is important that you tell the study staff about any symptoms or conditions that you experience.

Lopinavir
The major toxicity of lopinavir is diarrhoea and rise in lipids. Some patients also develop nausea and vomiting.

Saquinavir
Headaches is the most commonly reported side effect. Other commonly reported side-effects are gastrointestinal (diarrhoea and loose stools, nausea, and abdominal pain).

Copy made on: 29/07/2020

Subject initials_____

Ritonavir

Ritonavir is associated with liver toxicities, rises in triglycerides (fat in the blood), oral paraesthesias (tingling of the lips) and diarrhoea. These side effects are rare when at the dosing used in this study.

Saquinavir/ritonavir should be taken in conjunction with a meal. No food restrictions are necessary for the administration of lopinavir/ritonavir.

There is a possibility that your virus might become resistant to the treatment in this study. Your doctor will be following your progress very closely and will explain your treatment options to you if it becomes necessary.

11. What are the possible disadvantages and risks of taking part?

It is possible that if the treatment is given to pregnant women it will harm the unborn child. For female subjects, it is therefore very important that you do not become pregnant during this study. If you are a woman who is able to become pregnant, and choose to have sex during this study, you must agree to use a medically acceptable method of birth control throughout the study.

Certain brands of contraceptives that you take in pill form are not acceptable for this study due to possible interactions with protease inhibitors. Your doctor can tell you which brand is acceptable for you to use. Medically acceptable birth control methods include:

- Condom and spermicide
- Diaphragm and spermicide

Even if you use a medically acceptable birth control method, you could still become pregnant. You are aware that not having sex is the only certain way to prevent pregnancy. There is a slight chance that a pregnancy test could be wrong. If the pregnancy test is wrong, and you receive the study medication while pregnant, the drugs may harm an unborn baby. The effects of these drugs on an unborn baby are uncertain

12. What are the possible benefits of taking part?

It is not known nor is it guaranteed that you will receive any benefit from treatment on this study. It is possible, however, that treatment may provide benefit in stopping or decreasing the viral activity in your body. In addition, you will receive the benefit of health information and a chance to be in a research study to increase knowledge of HIV treatment for future sufferers.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor 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.

Also, 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.

Copy made on: 29/07/2020

Subject initials_____

14. What happens when the research study stops?

You have the right to leave this study at any time. If you do not want to be in this study, or if you leave this study, there will be no disadvantages or loss of benefits that you deserve. If your participation in this study stops for any reason, you will be asked to have the laboratory tests and physical examinations that are specified in the protocol for early termination.

If you wish to leave the study, please call a member of the research team:
Tony Drinkwater GRO-C bleep GRO-C
Zoë Cuthbertson GRO-C bleep GRO-C
Your participation in this study may be stopped at any time without you being asked. Your participation will be stopped if continued participation is not in your best interest; your compliance with dosing, visits, or other study procedures is poor, etc.

Since the study drugs are licensed for use in HIV disease you can continue your treatment after the research study stops.

15. What if something goes wrong?

In the event of an illness or injury that is reasonably determined to be related to the administration of the study medication, payment for reasonable medical and hospital costs may be provided. By signing this informed consent, you have not given up any of your legal rights.

16. Will my taking part in this study be kept confidential?

Every reasonable effort will be made to keep your medical records private. Only the study doctor and the research staff, sponsor (CHIP) or regulatory agencies and Ethics Committees will have access to inspect confidential data. By signing this consent, you hereby give permission for the doctors in charge of this study to release the information regarding, or obtained as a result of, your participation in this study to these entities.
All medical records that reveal your identity will remain private, except that they will be provided as noted above or as may be required by law.

17. What will happen to the results of the research study?

Results of the trial will be published after the statistical analysis has been performed and a report has been submitted to the relevant regulatory authorities. You will not be identified by name in any published results of this study.

18. Who is organising and funding the research?

The University of Copenhagen HIV Programme (CHIP) is funding this study.

Copy made on: 29/07/2020

Subject initials_____

19. Who has reviewed this study?

An Independent Ethics Committee, The Royal Free Hospital Local Research Ethics Committee, has reviewed the objectives and proposed conduct of the study and has given an approval/favourable opinion of it.

20. Contact for Further Information

If you or your relative(s) have any questions regarding the study or in the case of study related injuries you may contact Dr M Johnson on GRO-C

Thank you for considering this study.

Copy made on: 29/07/2020

Royal Free Hampstead NHS Trust

Royal Free Hospital
Pond Street
London NW3 2QG

CONSENT FORM

Title of project: A phase IV randomised, open-label, multicentre trial to evaluate the safety and efficacy of lopinavir/ritonavir (400/100 mg bid) versus saquinavir/ritonavir (1000/100 mg bid) in adult HIV-1 infected patients

Final Protocol, version 1.1 15th of February 2001

Acronym: MaxCmin2

Centre Number: .....

Patient number for this trial: GRO-B

Name of researcher: Dr Margaret Johnson

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.1 15th February 2001) for the above study and have had the opportunity to ask questions. GRO-B

2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. GRO-B

3. I understand that sections of any of my medical notes may be looked at by Responsible individuals from CHIP 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. GRO-B

4. I agree to take part in the above study. GRO-B

5. I wish for my General Practitioner to be informed of my participation in the study. ☒

6. I understand that should I become pregnant, think I might be pregnant, miss a period or it is late, have a change in my usual menstrual cycle, or I change my method of contraception I should immediately call the study doctor. ☒

GRO-B — GRO-C — 30/11/01

Name of patient — Date — Signature

GRO-C — 30/11/01 — GRO-C

Name of person taking consent (if different to researcher) — Date — Signature

Researcher — Date — Signature

Copy made on: 29/07/2020