18 May 2005

Mr R Murali
Director of Research and Development
Wrightington, Wigan & Leigh NHS Trust
Wrightington Hospital
Hall Lane
Appley Bridge
Wigan WN6 9EP

Dear Mr Murali

Title: A Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Crohn's Disease. M02-404
MREC ref: 03/5/049
LREC ref: M07/03/346

I would like to confirm that the above study has been inactive at this site since February 2004.

Please contact me on extension [redacted] if you have any queries.

I would be grateful if you could acknowledge receipt of the above information.

Yours sincerely

Sr. P. Johnson
Clinical Trials Department

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Received on 24.05.05

Received By J. Martin

Title R&D Co-ordinator

Protocol Number: M02-404
Subject Initials H ___ L ___

Royal Albert Edward Infirmary
Wigan Lane
Wigan
WN1 2NN

Subject Number_____

Information Sheet and Informed Consent Form

Short Title: A Multi-Center, Randomized, Placebo-Controlled Study of Adalimumab (D2E7) to Cause and Maintain Clinical Remission in Subjects with Crohn's Disease

Invitation To Take Part

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 or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. A leaflet entitled 'Medical Research and You' which gives information about medical research is available from Consumers for Ethics Research (CERES). If you would like a copy please ask for one.

Please take time to decide whether or not you wish to take part in this study. Thank you for reading this.

Purpose of Study

You have been asked to take part in a research study of an experimental (investigational) drug called adalimumab (D2E7) to treat Crohn's disease. An investigational drug is one that has not been approved by the U.S. Food and Drug Administration (FDA) or by regulatory authorities in other countries outside of the U.S.

The purpose of this study is to look at the safety and effectiveness of two different doses of D2E7 to cause and maintain remission in subjects with moderate to severe Crohn's disease.

Why have I been chosen?

You have Crohn's disease and with treatment, you are still experiencing signs and symptoms of Crohn's disease (stomach pain, diarrhoea, fatigue). We believe D2E7 may help patients with Crohn's disease that have not had complete relief of their symptoms with currently available medications. Approximately 830 subjects with Crohn's disease will participate in this study at 100 centres around the world.
It is up to you to decide whether or not to take part.

What will happen to me if I take part?

At the baseline visit you will receive two (2) injections of D2E7 and another injection of D2E7 at week 2. Then, at week 4 you will be put into one of three groups. There are two (2) dosing groups of D2E7 and one (1) placebo group that are being tested in this study. You will be put into a group at random (like the tossing of a coin) so you will have a 2 out of 3 chance of receiving D2E7 and a 1 out of 3 chance of receiving a placebo. A placebo is a dummy treatment that looks like the real thing but is not. It contains no active ingredient. Neither your study doctor nor you will know which group you are in, but the study doctor can find out if necessary.

After week 12, if your Crohn's disease becomes more active, you may be asked to visit your study doctor to find out if you meet certain criteria, so that your study doctor can give you D2E7 or may need to increase your medication.

Before treatment is started (screening visit), your medical history including any medications you take will be reviewed, you will have a physical examination, blood tests, urine test, a stool test, electrocardiogram (ECG - a test that studies the function of your heart), tuberculin PPD skin test (this is a test that determines whether or not you have been exposed to tuberculosis), and a chest X-ray. One chest X-ray will give you the same radiation exposure as a year's natural background radiation. If you are PPD positive, and further investigations show that you may nevertheless be included in the study, you may be asked to take anti-tuberculosis medication for a period of 6 months and you will have an additional chest x-ray at week 26. Approximately 15 ml (about ½ fl oz) of blood will be drawn at this visit. All of this will be done to be sure that you can go into the study.

If you can go into this study, you may need to stop certain medications you are currently taking. Your study doctor will tell you if you must stop using any of the medications you are currently taking.

During the study, you will visit your study doctor a total of 15 times over approximately 62 weeks (14 months and 2 weeks).

From the baseline visit to week 62 you will have a physical examination, blood (15ml or ½ fl oz) and urine tests. At baseline, week 4, 12, 26 and 56 you will fill in some questionnaires about your health. These will take you about half an hour to complete. At every study visit you will be asked about any problems you are having which may or may not be related to the study treatment and any change in the medications you are taking.

At each visit you will take a diary card home and fill out how many times you go to the toilet, how much pain you are experiencing, and your general well being and bring this to your next visit. You will also need to record when you take your medication on a dosing diary.

If you stop the study early, you will need to visit your study doctor and then come back after one-month for blood and urine tests and a physical examination.

What do I have to do?

- Come to your study visits as scheduled by your study doctor
- Take your study medication as instructed and return the used and unused study drug to the clinic at each visit
- Fill out your diary card completely and honestly and bring it to the clinic at each visit
- Fill out the questionnaires honestly
- Tell the study staff of any health problems you are having even if you don't think they are important
- Tell the study staff if you wish to stop being in the study and come back for the final visit
- You must not change any of your study medications without checking with your study doctor

What is the drug or procedure being tested?

D2E7 is man made in the laboratory but is the same as a natural human antibody. D2E7 is believed to work by blocking the inflammatory process, thus helping to relieve the signs and symptoms of Crohn's disease.

Your D2E7 must be stored in the refrigerator until shortly before injection. Never freeze your medication. All the liquid in the vial has to be drawn up in a syringe and injected under the skin. Please make sure that you change the injection sites regularly. All empty vials must be given back to your study doctor in the hospital when you next go to the clinic. You must also bring back used syringes to the hospital in the sharps containers provided.

The first time you get the medication you will receive two injections under the skin (in your abdomen or upper arm or under the skin in your thigh) and all of the other doses of study drug or placebo will be given as one injection of 0.8 ml (or ¼ fl oz). You, or a family member or friend, will be shown how to inject the study drug by a trained medical professional during the first 3 study visits.

What are the alternative treatment(s)?

Other treatments may be available to you as an alternative to D2E7. Your study doctor will discuss your treatment options with you.
You do not have to take part in this study to receive treatment for your condition.

What are the side effects/risks of taking part?

More than 2700 subjects with rheumatoid arthritis have been treated with D2E7. The majority of side effects experienced following administration of D2E7 were mild or moderate in severity.

The most common side effects with D2E7 were mild redness and/or itching, bruising, pain or swelling at the injection site. Other more common problems seen in patients have been infections, nausea, abdominal pain, headache, rash, accidental injury, back pain and increases in blood pressure and some changes in blood and urine test results.

There have been cases of infections such as the common cold, bronchitis and urinary tract infections. Because D2E7 reduces inflammation, it may make old virus or bacterial infections worse and acute infections might also be made worse. Fever may be reduced when you are ill so you may not realise that you have an infection. Wound healing may be slowed down. Subjects have

developed tuberculosis while taking D2E7. If you have a history of active tuberculosis, you should not enter this study.

Lymphomas (a type of tumour in the lymph nodes) have been observed in patients with rheumatoid arthritis treated with D2E7. Patients with rheumatoid arthritis may be at a higher risk for development of lymphoma than the general population. At this time, the role of D2E7 in the development of tumours is not known.

Minor allergic reactions and the formation of auto-antibodies have been observed in a few patients. More serious allergic reactions or rare cases of lupus-like syndrome resolved when D2E7 was stopped.

Some vaccines should not be given while receiving adalimumab. Please check with your study doctor before you receive any vaccines.

When you have a blood sample taken you may feel a slight pin prick which can cause temporary discomfort and there is a chance of bruising around the area. Very rarely a small clot or swelling may occur or it may bleed.

Taking part in this study may involve side effects that we do not know about. If you feel unwell at any time you should contact the study doctor responsible for your care in the study. Please ask your study doctor if you have any questions regarding any of the risks related to taking part in the study.

We do not know whether D2E7 has harmful effects on unborn children. Because of this, the study medication must not be given to pregnant women, breast feeding women or women who have children and who are not taking proper contraceptive precautions. All women capable of having children will be asked to use an effective method of barrier contraception for as long as they are in the study and for 90 days after the last dose. You will also be given pregnancy tests to make sure you are not pregnant.
Men who agree to participate in this study should practice adequate means of contraception for the entire time that they are participating in the study and for 90 days after the last dose.
Your study doctor will talk to you about this in more detail.

What about compensation?

In the event of an injury occurring as a result of your taking part in this study, Abbott Laboratories have agreed to abide by the Association of British Pharmaceutical Industry (ABPI) Guidelines on Compensation 1991. By signing this form you are not losing any of your legal rights.

information collected as part of the study will be transferred to representatives of Abbott Laboratories, its related companies and agents, other companies working with Abbott, and governmental drug regulatory agencies. This information may be transferred to these organisations by computer. These organisations may be located in other countries, including the United States. Countries outside the European Union (EU) may not have laws that protect your privacy to the same extent as European law, but Abbott will take all reasonable steps to protect your privacy. This study is being conducted according to the requirements of the UK Data Protection Act 1998 Part II. By signing the consent form you are agreeing that your medical information from the study may be sent outside the EU for analysis in a form that does not include your name.

Under the Access to Health Records Act (1990), you may ask to see your study records, however the study treatment may need to remain unknown until after the study data analysis is completed.

What do you do with my information?

The information collected in this study will be processed to meet the purpose of the clinical study. Information may be used for seeking approval from governmental drug agencies to market the medicine. It may also be used in reports of the study or for scientific presentations. You will not be identified in any such publication. Abbott or its representatives may also use the information from this study, which relates to you, for future medical research either in this field, or in a new area (but only with further ethics committee approval).

What if I want to stop taking part in this study?

Your participation is completely voluntary and you can decide not to take part in the study at any time. This will not affect your care in any way, either now or in the future. If your personal circumstances change and you no longer wish to take part you may leave at any time. If you choose to stop taking part in the trial, your study doctor will make arrangements for your care to continue. You do not have to give a reason for leaving the study and this will not affect how your study doctor cares for you. If at any time you decide to stop taking part in the study, you should talk to the study doctor so that you can stop safely. If you stop the study early it is in your own interests to return to your study doctor for a check up.

Your study doctor, the ethics committee, the governmental drug regulatory agencies, or Abbott Laboratories may stop the study at any time with or

What are the possible benefits of taking part?

The information that is obtained during this study may be useful scientifically and thus may help us treat future subjects with Crohn's disease better. We hope that treatment will help you, however this cannot be guaranteed.
It is possible that the signs and symptoms of your Crohn's disease may improve and your disease may go into remission. However, no one can predict whether you will benefit from D2E7 treatment. It is possible that your condition may not improve or may worsen while taking part in this study.

What if new information becomes available?

If we find out any more information on D2E7 you will be told in writing. This may change the way you feel about taking part in the study and you are free to withdraw at any time. If you decide to continue in the study you will be asked to sign a new (updated) consent form to confirm that this new information has been explained to you.

What happens when the research study stops?

When you leave the study, the study medication will be stopped and your study doctor will discuss other treatments with you.

What about confidentiality?

If you wish to take part in the study, you must agree that we will let your GP know. This is done to make sure all doctors having anything to do with your care are aware of the medicines or treatments that you are taking. They can also tell us if there is any medical reason why you should not take part in the study. Your hospital notes will also state that you are in this study.

Representatives of Abbott Laboratories (the sponsor for this study), its related companies, and agents will need to inspect your health records, relevant to this study. In certain circumstances your records or results may be looked at by a governmental drug regulatory agency for purposes of analysing the results or checking that the study is being done correctly. By signing the consent form, you are agreeing to let these people see your medical records. Records that identify you by name will be kept confidential. If the study results are published, the published report will not include your name.

Any information that may leave the hospital will have your name and address removed and you will only be identified by your initials and study number. The

without your permission. Your study doctor may choose to take you out of the study if it is in your best interest or because you may not be following the instructions properly.

If you withdraw from the study you can also ask in writing to stop further access to your personal information. However any request does not apply to data already collected as part of the study.

Payment for the study

Abbott Laboratories is providing your hospital with funding to cover the costs of carrying out this study. You will be offered travel expenses to cover the cost for attending visits. You will not be paid for taking part in the study.

Ethics Committee review

The Wigan, Wrightington and Leigh Ethics Committee has reviewed and approved this study.

Who do I call if I have questions or problems?

Please contact the study doctor below at any time, if you would like more information about any part of this study or if you would like more information about what to do in the case of a study related injury, or if you would like to see the ABPI guidelines or receive a copy of Consumers for Ethics Research (CERES) leaflet.

Doctor:	*Dr Phillip Bliss*
Address:	*RAEI, Wigan Lane, Wigan, WN1 2NN*
Telephone:	*01942 822 449*

Royal Albert Edward Infirmary
Wigan Lane
Wigan
WN1 2NN

Protocol Number: M02-404
Subject Initials HL Subject Number_____

SUBJECT CONSENT FORM

	Please initial each box
1. I confirm that I have read this information sheet dated 2 July 2003 (version 2) and all my questions regarding participation in this research study have been answered.	HL
2. I authorize access to my medical records by Abbott Laboratories, its related companies, and their agents, the regulatory authorities.	HL
3. I understand that I will receive a copy of this signed and dated consent form.	HL
4. I understand that this study is being conducted according to the requirements of the UK Data Protection Act 1998 (Part II) and I agree that my medical information may be sent outside the EU for analysis in a form that does not include my name.	HL
5. I agree that information from this study may be used for future research (but only with agreement from the ethics committee if the research is unrelated to this field).	HL
6. I understand that my participation in this study is voluntary, that I am free to withdraw at any time without giving any reason and that my medical care or legal rights have not been affected.	HL
7. I understand that if I do decide to withdraw from the study my data will not be destroyed.	HL
8. I am aware that my GP will be informed that I am taking part in this study.	HL
9. I agree to take part in this study.	HL

H [redacted]	18/5/04	H [redacted]
Subject Name (print)	Date	Subject Signature (or legally acceptable representative)
P. Bliss	18/5/04	
Investigator Name (print)	Date	Investigator Signature

1 for subject; 1 for investigator; 1 to be kept with hospital notes