

PAREXEL International Ltd (PAREXEL)  
**Clinical Pharmacology Research Unit**  
**Northwick Park Hospital**  
INFORMED CONSENT FORM

*Please initial each box*

1. I confirm that I have read and understood the informed consent form (version 02, dated 9 February 2008, pages 1-2) and separate information sheet (version 02, dated 9 February 2008, pages 1-11) and have been given the opportunity to ask questions and agree to participate in the above study, which is being conducted on behalf of TeGenero AG (who is the Sponsor of this study). I understand that an independent Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA) have approved this study.
2. Dr Daniel Bradford, the Principal Investigator, or his deputy has explained the nature and purpose of the study and has provided me with the information sheet.
3. I have read the information sheet relating to blood borne viruses (HIV and hepatitis B and C) (Version 4, dated 8 June 2005) and consent to be tested for these viruses.
4. I authorise you to contact other drug trial units and enquire about my participation in/registration for studies elsewhere.
5. I agree that one of the Unit's Physicians may contact my General Practitioner and I authorise my General Practitioner to divulge, to one of the Unit Physicians, any information deemed relevant regarding my suitability to participate in volunteer drug trials.
6. It has been explained to me that the procedures being tested in this First Time in Man study may involve risks to me, which are currently unforeseeable.
7. I have read and understand the compensation arrangements for this study
8. I understand that my rights to compensation may be affected if I fail to disclose to the Principal Investigator or deputy any relevant information which may affect my participation in this study, or if I fail to adhere to the requirements of the study.
9. I agree that I will not seek to restrict the use to which the results of the study may be put. I accept that my records or results may be disclosed to regulatory authorities for medicines in the UK and elsewhere.
10. I understand that having signed the consent form I do not have to participate in the study and can withdraw at any time without giving a reason and my rights will not be affected.

Protocol Number: **TGN1412-HV**

PAREXEL Project Number: **68419**

Name of Subject:

Date of Birth:

Subject's Unique ID No:

Address;

Signature

Date

\_\_\_\_\_  
Name of person taking consent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (dd/mmm/yy)

\_\_\_\_\_  
Time (24 hr clock)

## INFORMATION SHEET

### **A Phase-I, Single-Centre, Double-Blind, Randomised, Placebo Controlled, Single Escalating-Dose Study To Assess The Safety, Pharmacokinetics, Pharmacodynamics And Immunogenicity Of TGN1412 Administered Intravenously To Healthy Volunteers**

(A first-in-man study to investigate the effects in healthy male volunteers of single doses of a new drug for the potential treatment of various inflammatory diseases.)

#### Invitation

You are being invited to take part in a research study. Before you decide to take part 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 others 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 will be available for you to read in reception at the Unit.

\*\*\*For possible side effects please refer to page 7 of this document\*\*\*

#### Introduction

This study will involve the use of a new compound (TGN1412, described as the study drug in the remainder of this consent form) being developed by TeGenero AG (The Sponsor of this study) for the treatment of various inflammatory diseases such as rheumatoid arthritis, and possibly also for a particular type of leukaemia. This study drug is a “monoclonal antibody” which means that it is an antibody (a naturally produced protein) that has been designed by scientists to target a particular type of cell — in this case a type of white blood cell called T cells. The PAREXEL Clinical Pharmacology Research Unit is based at Northwick Park Hospital (but is independent of the hospital) and is being paid by TeGenero AG to conduct this study.

This study is a First Time Into Human study and will test the safety and the effects on the body with varying doses of the study drug. Preliminary data from animal studies demonstrated that the study drug was safe and well tolerated.

A total of 32 healthy male subjects, aged between 18 — 40 years inclusive, will be enrolled into this study. The study is divided into four groups, each containing 8 volunteers. A volunteer will only be allowed to take part in one group of this study.

You will be required to attend the unit for two screening visits and one treatment period lasting for 3 nights. You will then be required to attend the unit for out-patient visits on Days 4, 5, 6, 8, 10, 12, 15, 18, 22, 29 and 36, with final assessments taking place at the

follow up visit on Day 43. The maximum length of time (from screening to follow up) that you will be required to take part in the study will be approximately 10 weeks.

The planned doses for each group will be 0.1 0.5, 2.0 and 5.0 mg per kg of body weight administered intravenously by injection into a vein. Doses will be investigated in ascending order, starting from group 1. and the next scheduled dose will be confirmed only after the review of all relevant safety data of the preceding group. Therefore, except for the first dose, all other doses may be subject to change based on this safety data. It may also be decided to repeat a dose level or give a lower dose than that which was given in the previous group, based on this data.

In all cases, volunteers will be 'randomized' to receive either a single dose of the study drug or a placebo ('dummy drug' not containing active medicine) as an intravenous infusion on day 1. Both the study drug and placebo will look identical, so you will not know whether you are receiving the study drug or placebo. Randomisation means that the participants are put into treatment groups by chance, the groups are selected by a computer that holds no information about the individual participants. Because the study is 'double-blind', neither the volunteers nor the PAREXEL staff will know who is on 'active' and who is on placebo medication. However, staff will be able to quickly find out this information, if required.

This study is for research purposes only and as a volunteer you will receive no therapeutic benefit from taking part.

During the conduct of the study a number of blood, urine and other tests will be performed. These tests may rarely reveal a pre-existing medical condition. If any relevant abnormality is detected, a member of the unit medical staff will discuss it with you in private and, with your consent, appropriate medical management will be recommended in consultation with your General Practitioner.

#### Purpose of study

The main aim of this study is to assess the safety and tolerability of the study drug when administered to healthy subjects. The level of study drug in the bloodstream will also be measured, which will help identify suitable dose levels for future clinical studies. In addition, further blood samples will be taken to help establish how effective the study drug is.

#### Volunteer Screening Visit

You will be asked to attend the PAREXEL Clinical Pharmacology Research Unit based at Northwick Park Hospital on two separate occasions in the 4 weeks before the first study day, **having fasted from all food and drink with the exception of water for at least 10 hours prior to arrival**. At the first visit, the duration and nature of the study will be explained to you in detail. If you wish to take part, you will be asked to sign a consent form and your General Practitioner will be notified of your intention to participate and asked to complete a questionnaire regarding your health and suitability for the study. You may decline to participate at any stage.

At the screening visit a doctor will carry out a physical examination, and check your medical history. An ECG (a test of your hearts rhythm), blood pressure and pulse measurement will also be taken.

Blood and urine samples for routine analysis will also be taken. This will include a urine test for alcohol and drugs (cannabinoids, amphetamines, barbiturates, benzodiazepines, cocaine and opiates). In addition, you will have blood samples taken which will indicate if you are predisposed to “autoimmune disease”, (where a persons immune system attacks the body’s own tissue) e.g. rheumatoid arthritis.

A blood test for hepatitis B and C (Viruses that cause inflammation of the liver) and HIV (the virus that causes AIDS) will be carried out to protect and ensure the safety and wellbeing of both yourself, other volunteers, the Investigator and staff members from infection through bodily fluids and will not be taken for any other reason. Should any of the tests be out of the range as specified for this study, you may sometimes be asked to return to the Unit and provide an additional sample for repeat testing. Specific details about any repeat samples required will not normally be discussed over the telephone but will be addressed when you attend the Unit.

If any of your blood or urine results are abnormal, you may not be able to participate. If these results are deemed to be clinically significant, we will forward a copy of these results to your GP after obtaining your permission and advise you to visit your GP for further evaluation,

This ‘screening visit’ is designed to assess all potential trial volunteers, and to ensure that the trial is as safe as possible — those for whom the trial would not be safe are literally ‘screened out.’ Therefore it is important that you are in good health at this visit. One of the commonest reasons for being rejected at screening is having elevated blood liver function tests (sometimes called LFTs) as a healthy liver is essential for clearing drugs from your system and detoxifying you. Liver test results are raised by alcohol and also by exercise, often for several days. This is why we ask you to avoid alcohol and exercise before screening, so we can assess your liver properly.

If all of your blood and urine results are satisfactory, you may be invited to take part in the study. Please note, however, that a place on the study cannot be guaranteed and that an invitation to be screened does not oblige PAREXEL to include you in this study, or to make any payments to you. Please be advised that you should not attend the Unit for a study until a member of the screening team has spoken to you in person and confirmed your place on the study.

You may be asked to be a reserve volunteer, as we usually need to have additional volunteers on standby in case of volunteer non-attendance, exclusion or last minute withdrawal. Reserve volunteers are selected based on safety results, or where these are equal, on a first-screened-first-enrolled basis. Reserves need only to stay until dosing is completed, are paid for their time. and can usually take part in / be screened for another study straight away for which they will be given preference. The usual practice is for reserve volunteers to join the next group of the same study, to avoid having to re-screen.

In every case the final decision on ‘included’ and ‘reserve’ volunteers will be made by the medical staff, based entirely on safety.

Study Procedures

You will be asked to arrive at the PAREXEL Clinical Pharmacology Research Unit based at Northwick Park Hospital at 11am, the day before your study group starts (Day -1).

Urine alcohol and drugs of abuse tests will then be carried out to ensure that you have complied with the study restrictions. You will be examined by a doctor, including examination of your lymph nodes (sometimes called 'glands', in neck, underarms and groin), you will be weighed and you will have blood and urine samples taken for routine analysis and to indicate your own natural levels of certain 'immunity' blood cells. You will be given an evening snack, after which you will fast overnight from 22:00 from all food and drink with the exception of water.

On the morning of Day 1, before you receive the dose of study medication, you will have the following procedures performed: Vital signs, EGG, a baseline blood sample for study drug levels, as well as numerous blood samples to assess your immunological profile. Then, at the allocated time (approximately between 08:00 & 10:00), you will be given your study medication in the form of an intravenous infusion (where the study drug is administered directly into a vein). For practical reasons, the time of dosing will be staggered. You will not be given any food until 4 hours post dose, but you will be allowed to drink water as and when you require,

On Day 1 (after dosing) and up to discharge from the unit on Day 3, you will have the following assessments performed at specified times: Vital signs, body temperature, EGG, examination of your lymph nodes, as well as routine blood and urine sampling for the continued determination of your well-being. Blood samples will also be collected for determining how much study drug is present in your blood stream.

You will then be required to return to the unit for outpatient visits (on Days 4, 5, 6, 8, 10, 12, 15, 18, 22, 29 and 36) when repeat assessments will be performed. Each of these visits should take no more than an hour, and will usually take place in the morning at around the time you were dosed.

The time-points for the blood/urine samples may change or additional samples may be collected following review of the blood samples from previous Groups.

The total amount of blood to be taken for this study (including routine analysis) will be no more than 600 ml over the entire two-month period. This is slightly more than the volume given as a single donation at the Blood Transfusion Service (450 ml) and we do not foresee any ill effects from this.

Post-Study

At the end of the study (on Day 43) you will be asked to return to the Unit to give blood and urine samples for routine analysis. These tests sometimes need repeating which would involve an additional visit to the Unit to provide another sample.

You are not discharged from the study until all the results are satisfactory and it is only at this stage that any payment request will be made.

Volunteer Restrictions

If you have participated in a study within the last 4 months, either here or at other sites, you should talk to a Unit Physician because you may not be suitable for this study.

You must refrain from taking any medication at all during the 2 weeks prior to the dosing occasion on Day 1- This includes herbal, 'natural' and even homeopathic supplements, as well as vitamins, minerals, eye/ear/nose drops and skin creams. A substance does not need to be given by a doctor to be a medicine' - if in doubt, please do not use anything at all from screening until your post-study visit.

You should not stop any regular prescribed medication or discontinue any medication where necessary without first discussing this with your Doctor or the Unit Physician. Please notify a Unit Physician if it has been necessary to take any medication so that we can confirm whether or not this will have any effect on your participation in the study.

You must refrain from using a sauna, sunbathing or undertaking any strenuous exercise (including competitive sport) from 72 hours before screening, prior to the dosing occasion on Day 1 until the end of study examination on Day 4 This is because of the effect that exercise has on your blood tests, making them difficult to 'read' as detailed above

You must refrain from alcohol for 48 hours prior to and during each study visit. Additionally, you should consume no more than 4 units of alcohol per day from the time of the pre study screening visit until the post study visit (1 unit = 1 measure of spirits / 1 glass of wine / 1/2 pint of beer).

You will be required to refrain from food and drink that contains caffeine (coffee, tea, chocolate, cola) after entering and until you leave the Unit.

As this is a **First Time in Man** study, you should abstain from unprotected sexual intercourse for at least 3 months after receiving the study medication, as the risk of the study drug to the unborn foetus is unknown. It is recommended that barrier protection is used. This applies to both men and women.

Smoking is not permitted within the Unit or the hospital.

Volunteers should maintain a normal diet and activities throughout the study.

Possible Side Effects

There is no definitive information on the side effects of this drug in man. As this is only the first time this drug will be given to man, this study may involve risks that are currently unforeseen. No significant side effects have been seen in the animal studies, and although these are not a precise indicator of what will happen in humans, they give some indications of the possible side effects.

Expert advice from immunologists has been sought in designing the protocol to minimise your risks, including a robust screening process that takes into account your immune status, and repeated thorough assessments of immune function.

It is possible that you will not experience any side effects at all, as the doses used in early human studies are always very small, and increased only gradually, but the following unintended effects may theoretically be encountered during any trial with a monoclonal antibody drug, though they did not occur even at the highest tested doses in animals: immunosuppression (increasing susceptibility to infection, very unlikely after a single-dose), autoimmunity (antibodies being made by your own body against the drug), cytokine release (causing a hives-like allergic reaction), or even anaphylaxis (a generalised allergic reaction that can be life-threatening). Drugs of this type can also cause swelling of the lymph glands, so you will be regularly checked for this. Less specific symptoms such as headache, dizziness and nausea are more common in all drug trials.

Risk of anaphylaxis applies to all studies at PAREXEL, with drugs at every stage of development, and the staff are well trained in anticipation of this (unlikely) possibility. Anaphylaxis could occur any time you encounter any new drug, cosmetic or even foodstuff in a restaurant (peanuts and shellfish are famous for causing it).

You are instructed to let the staff know without delay if you experience any 'side-effects' while on this drug trial. You will be closely monitored during the trial for any evidence of these effects during the study. If the effects are of concern, you may be withdrawn from the study, in the interests of your safety - the symptoms will be treated as appropriate.

You may experience minor discomfort from the blood sampling procedures, and occasionally some bruising or irritation of the veins used for blood sampling. These effects normally resolve completely in a few days. Some individuals may experience slight skin irritation from the ECG electrodes, but this is generally mild and resolves within a few days.

Please be aware that any drug can cause a serious allergic reaction in susceptible individuals. For example, penicillin and even aspirin can be life-threatening to some people. It is essential for this reason that you are honest regarding your past medical history, to allow our doctors to keep this trial as safe as possible.



Further information may become available during the course of the study and, if this information is relevant, you will be kept informed. If, after a written and verbal explanation of this additional information, you are happy to continue in the study, you will be asked to sign a further consent form.

Volunteer Obligations

As a volunteer you must:

- Adhere to the restrictions specified above.
- Notify the Investigator if you are unable, in any way, to follow the study procedures
- Notify the Investigator if you feel at all unwell, at any time during the study. If this occurs while you are not in the Unit, you must make every effort to contact the Investigator or the Study Physician (whose name and contact number will be provided on a card for you to keep for the duration of the study, please ensure you keep this card with you at all times). This also applies to time outside normal working hours.
- Notify the Investigator if you are required to take ANY MEDICATION during the study, for example if your own doctor prescribes antibiotics for an infection. You should of course also remind any doctors treating you that you are currently in a drug trial.

It is vital that you adhere to the requirements stated in this consent form. In particular, if your urine tests positive for drugs or you deliberately disregard any instructions given to you during the study period, you may be asked to leave the study and will not be invited to take part in future studies. Furthermore, part of the payment will be deducted as a penalty.

The information and any materials or items that you are given about or during the study such as information regarding the study drug or the type of study being performed -should be considered the confidential business information of the Study Sponsor, TeGenero AG. You are of course free to discuss such information under confidence with your doctor or with your friends and family while considering whether to participate in this study or at any time when discussing your present or future healthcare.

Injury and Compensation

TeGenero AG (the Study Sponsor) agrees to comply with the current guidelines laid down by the ASPI (The Association of the British Pharmaceutical Industry) regarding injury and compensation. These guidelines state:

1. In the event of you suffering any significant deterioration in health or well-being caused directly by your participation in the study, compensation will be paid to you by the Sponsor,
2. Compensation will be paid to you without you having to prove either that the injury arose through negligence or that the product was defective in the sense that it did not fulfil a reasonable expectation of safety.
3. The amount of such compensation will be calculated by reference to the amount of damages commonly awarded for similar injuries by an English court if liability is admitted- Please note that any compensation may be reduced to the extent that you by reason of contributory fault, are partly responsible for the injury (or where you have received equivalent payment for such injury under any policy of insurance effected by the company for your benefit).
4. Any dispute or disagreement arising out of this undertaking will be referred to an arbitrator to be agreed between you and the Study Sponsor or, in the absence of agreement, to be appointed by the President of the Royal College of Physicians of London with power in the arbitrator to consult a barrister or trial lawyer of at least 10 years standing in respect of any issue of law including the amount of damages to be awarded as payment of compensation.
5. Payment will be made as soon as is practicable

Should you suffer injury either during or after the study, and believe it to be a result of your participation in the study, then please contact the PAREXEL Unit medical staff at the earliest opportunity. All necessary actions to rectify the injury will be made under the guidance of the PAREXEL Unit medical staff.

#### Data Protection

As a patient taking part in this clinical study, personal information about you will be collected by your doctors, study nurses, pharmacists and other PAREXEL personnel. This personal information will include information about your health and your demographic details (such as your date of birth, your sex, and your ethnic origin). The Sponsor of this clinical study, and PAREXEL International Limited are legally obliged to inform you of the following:

1. Throughout this study your doctors and nurses will record information about you in forms provided by us (known as "case report forms"). All records and all other information about you entered into the case report forms may be identified by your initials and a subject number, not your full name.
2. Information collected about you for the study will be processed by us and may be included in reports which will be submitted to authorities (either in the United Kingdom, Europe, the United States of America or in any other country in the world) so that one day the study medicine may be available to all patients suffering from the illness this drug treats. As part of the data processing, which

will result from this clinical study, your information may also be passed to authorised personnel within:

- TeGenero AG, PAREXEL International Limited and its group of companies, regulatory authorities, and
- The Ethics Review Committee.

Such authorised personnel may inspect your records and information and take copies.

3. Some of the countries to which your information may be passed may not have the same level of data protection as the United Kingdom. All reasonable steps will be taken by us to protect your information.
4. Your information will only be used for the purposes stated above as explained to you by Dr Daniel Bradford, the Principal Investigator, or his deputy, and will be kept no longer than necessary and (unless required by law) will not be disclosed to people other than mentioned above.
5. You have certain rights which may allow you to have access to data held about you, and to object or prevent certain processing of your information if it will cause you damage or distress. For further details on your rights and how you can enforce them, you should contact the Data Protection Registrar's office (now known as The Office of the Information Commissioner, Executive Department, Water Lane, Wycliffe House, Wilmslow, Cheshire SK9 5AF, [www.dataprotection.gov.uk](http://www.dataprotection.gov.uk)).

Your National Insurance number (if you are a UK citizen) or your passport number and country of origin (if you are not a UK citizen) will be entered into a database. If you go on to take part in a study, the date on which you receive your final dose of study medicine will also be entered- Your participation in one of our studies may be discussed with other medicines research units. These measures are intended to prevent you from being harmed by taking part in too many studies.

#### General Points

For your time, and to compensate for any inconvenience, a payment of £2000 will be made on completion of the study. If you are required to come back to the Unit for extra blood samples to check the levels of study drug in your blood, you will receive £30.00 per visit. You will not receive further payment for additional visits for routine blood and urine safety samples.

N.B. A study is not completed until the results of your post study blood/urine samples are considered acceptable.

- If you withdraw from the study prior to completion, you will be paid on a proportional basis.
- If you leave the study and exercise your right not to give a reason, or are required to leave the study for non-compliance, no payment need be made to you. This will be at the discretion of the Investigator.

- You should be aware that your study payment will be reduced if you fail to comply with any of the restrictions specified above or break any of the Unit rules. The payment reduction will be made at the discretion of the study personnel, and may amount to 10% per misdemeanour. A copy of these rules may be provided to you at your screening visit and is posted on notice boards within the Unit.
- If you attend the Unit as a reserve and are not subsequently dosed you will receive £150.
- The payment will be made in the form of a crossed cheque that must be paid into a bank account bearing your name. You are responsible for paying tax on it if appropriate to your circumstances. Please note that you will be liable for any cancellation charges incurred for lost cheques.

Your participation in the study may be stopped for any of the following reasons:

- Failure to comply with the Investigator's instructions.
- A serious adverse event, which may require treatment or observation.
- The Investigator decides it is in the best interest of your health and welfare to discontinue.
- Insufficient enrolment in the study.
- The Sponsor stops development of the investigational drug

Please read your consent form carefully and if you have any questions please do not hesitate to ask. You will be given a copy to take away with you.

Any new information that becomes available during the course of the study and may relate to your willingness to continue participation will be explained to you. You will also be given the opportunity to ask questions and consider whether you are happy to continue in the study.

The procedures being tested in this study may involve risks to you that are currently unforeseeable. A description of all reasonably foreseeable risks or discomforts is contained within this information sheet.

Your participation in this study is entirely voluntary and you will receive no benefit other than payment for your participation. Having signed the consent form you do not have to participate in the study and can withdraw at any time without giving a reason. You may be withdrawn from the study if it is considered necessary by the Investigators. If you decide to withdraw from the study you should contact the Investigator and discuss any necessary procedures required to discontinue participation. If you hold a medical or travel insurance policy, you may wish to inform your insurer of your intended participation in this trial, in case it affects your policy cover.

This study has been carefully reviewed and approved by an Independent Research Ethics Committee. One of the obligations of the Committee is to safeguard the interests of volunteers. If you have any point of concern, before during or after the study, you can discuss this with the Principal Investigator or Unit Medical Director, then you may approach the Ethics Committee who have approved your study by writing to them. Contact details will be available from the Principal Investigator. This study has also

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been granted approval by the Medicines and Healthcare Products Regulatory Agency (MHRA) the government appointed agency for the United Kingdom. The MHRA are also responsible for evaluating this unit and granting the unit approval to carry out Clinical Trial activity.

If you have any queries regarding blood/urine results or participation in this study, you should contact one of the two people listed below:

Screening Co-ordinator

Tel: 01895 814 688

Dr Daniel Bradford  
Principal Investigator

Tel: 01895 614655

These telephone numbers are direct lines and, if there is no answer, you should wait until you are connected to the voice-mail system and leave a message (including a contact number). Your call will be returned as soon as possible.

If you are not contacted within 24 hours please telephone: 01895 614851. This number connects you to reception during office hours and to a voice-mail system (which is regularly checked) after hours.

You can always speak to the on-call doctor on the 24-hour/7-day emergency line, but please use this only when necessary:

Emergency 24 hour contact

Tel: 07740 631222