PAREXEL.

Clinical Trial Protocol

A PHASE-I, SINGLE-CENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, SINGLE ESCALATING-DOSE STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, PHARMACO-DYNAMICS AND IMMUNOGENICITY OF TGN1412 ADMINISTERED INTRAVENOUSLY TO HEALTHY VOLUNTEERS

Sponsors study code	TGN1412-HV
PAREXEL Study code	68419
EudraCT-No	2005-003371-21
Developmental Phase	I
Sponsor	TeGenero AG Science Park Friedrich-Bergius-Ring 15 97076 Würzburg Phone: +49(0) 931-35962-0 Fax: +49(0) 931-35962-11
Investigator *	[redacted] PAREXEL International Parexel CPRU, Floor 7 Main Ward Block, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ [redacted]
Version Number	2.0
Document Date	21 December 2005

* Name(s) withheld under sections 40 and 38 of the FOI Act as, in the MHRA's view, the public interest in disclosure is not outweighed by the public interest in maintaining that confidence

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Signature Page

A PHASE-I, SINGLE-CENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, ESCALATING DOSE GROUP STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND IMMUNOGENICITY OF SINGLE DOSES OF TGN1412 ADMINISTERED INTRAVENOUSLY TO HEALTHY VOLUNTEERS

Sponsor's Study code:	TGN1412-HV
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We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct this study.

*

[redacted]
PAREXEL International

21 DEC 2005
Date

[redacted]
TeGenero AG

21/12/05
Date

[redacted]
Signature

* see note on page 1

Protocol Synopsis

Title	A PHASE-I, SINGLE-CENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, ESCALATING DOSE GROUP STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND IMMUNOGENICITY OF SINGLE DOSES OF TGN1412 ADMINISTERED INTRAVENOUSLY TO HEALTHY VOLUNTEERS
PAREXEL Study Code	68419
Sponsor's Study Code	TGN1412-HV
EudraCT-No.	2005-003371-21
Study Drug	TGN1412
Sponsor	TeGenero AG
Study Phase	I
Study Site	PAREXEL International Parexel CPRU, Floor 7 Main Ward Block, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ [redacted]
[redacted]	[redacted]
Study Objectives	Primary objectives: • Assessment of the safety and tolerability of ascending single intravenous doses of TGN1412 in separate cohorts of healthy volunteers. • Determination of the pharmacokinetics of single intravenous doses of TGN1412. Secondary objectives: • Determination of the effect of TGN1412 on lymphocyte subsets. • Assessment of the cytokine profile following administration of TGN1412. • Assessment of anti-TGN1412 antibodies up to seven weeks post-dose.
Study Design	Single-centre, randomised, double-blind, placebo-controlled, single ascending-dose escalation trial. Dose escalation to the next dose level will proceed following satisfactory review of safety data from at least fourteen days following each dosing.
Planned Sample Size	Total: 32 subjects, n=8 per group
Study Population	Healthy male subjects aged 18 – 40 years
Randomisation	Per group: n=6: active treatment; n=2: placebo
Reference Therapy	Placebo
Dose/Route/Duration of Treatment	Four single doses, administered intravenously per infusion: 0.1, 0.5, 2.0 and 5.0 mg/kg body weight
Duration of Study	In total: 107 days, at least 45 and up to 64 days per subject

* withheld under sections 40 and 36 of the FOI Act - see page 1.

Criteria for Evaluation	Section withheld under section 43(2) of the FOI Act as, in the MHRA's view, disclosure would, or would be likely to, prejudice the commercial interests of TeGenero or associated third parties. In the Agency's view the public interest in disclosure does not outweigh the public interest in withholding the information.
Statistical Methods	Safety: All parameters will be listed and summarised descriptively. Changes to baseline will be calculated, if appropriate. PK: Drug concentrations and all derived parameters will be listed and summarised descriptively. PD: Dose-response relationship will be explored on a descriptive level by means of an appropriate ANCOVA model with fixed factor 'treatment' and individual baseline measurements as covariate.

List of Personnel

Sponsor

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Sponsor's contact persons	[redacted] *
Sponsor's contact person in case of serious adverse events	[redacted] *
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[redacted]	[redacted] *

* see note on page 1. This also refers to all information on pages 6 and 7, so these are not included.

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Abbreviations

λ_z	Apparent terminal elimination rate constant
AE(s)	Adverse event(s)
ALT (GPT)	Alanine amino transferase
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
AST (GOT)	Aspartate amino transferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration vs. time curve; subscripts denote the time interval the AUC was calculated for
b.w.	Body weight
B-CLL	B-cell Chronic Lymphocytic Leukaemia
BLQ	Below the limit of quantification
BMI	Body mass index
CDR	Complementarity-determining region
CD-XY	Cluster of differentiation of leukocytes
CHO	Enzyme from Chinese hamster ovary cell line
CK	Creatine kinase
CL	Total clearance
C_{max}	Maximum plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CPR	C-reactive protein
CPRU	Clinical Pharmacology Research Unit
CRF	Case Report Form
CTLA-4	Cytotoxic T-lymphozyte-associated protein 4
CV%	Coefficient of Variation
E	Number of events
e.g.	For example
EBV-load	Epstein-Barr virus load
EC	Ethics Committee
ECG	Electrocardiogram
EDTA	Ethylenediamino tretraacetic acid
ELISA	Enzyme-Linked Immunosorbent Assay Test
EMEA	European Medicines Evaluation Agency
ESI-TOF	Electro spray ionisation time-of-flight
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FIM	First in man
FoxP3	Forkhead box transcription factor P3
G-GT	Gamma glutamyl transferase
GATA-3	Trans-acting T-cell specific transcription factor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Heavy chain
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
i.a.	Intra-arterial
i.e.	Id est
i.v.	Intravenous
IB/CIB	Investigator's Brochure / Clinical Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-XY	Type of interleukin
INR	International Normalized Ratio For Prothrombin Activity
Ki-67	Nuclear antigen, tumour growth marker
LC	Light chain
LOQ	Lower limit of quantification
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MRT	Mean residence time
MTD	Maximum tolerated dose
N, n	Number(s)
NACl	Natrium chloride
No.	Number
NOAEL	No-observed-adverse-effect level
OPS	Perfusor syringe
p.v.	Perivenous
PBMC	Peripheral blood mononuclear cells
PBS	FACS Puffer
PD	Pharmacodynamic(s)
pH	Hydrogen ion concentration
PK	Pharmacokinetic(s)
RA	Rheumatoid arthritis
RBC	Red blood cell count
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
$T_{1/2}$, $t_{1/2}$	Apparent terminal elimination half-life
T-bet	Th-1-specific T-box transcription factor
T-cell	Thymus dependent cell
TCR	T-cell antigen receptor
[redacted]	
TH2 T-cell	Subset of helper inducer T-Lymphocytes
T_{max}, t_{max}	Time to reach peak concentration
TNF	Tumour necrosis factor
$V_{\lambda z}$	Terminal rate constant
V_1-V_6	Six pre-cordial lead
vs.	Versus
V_{ss}	Volume of distribution at steady state

* information withheld under S38 of the FOI Act as, in the MHRA's view, the public interest in disclosure is not outweighed by the public interest in withholding the information

WBC	White blood cell count
WHO	World Health Organisation

1. Introduction

1.1. Background

TGN1412 is an agonistic anti-CD28 monoclonal antibody, developed as a therapeutic agent for various diseases in which T-cells are involved in the pathogenesis of chronic inflammation or haematological malignancies such as leukaemia. This antibody is a recombinantly expressed humanized monoclonal antibody that specifically binds CD28 expressed on human T-cells. TGN1412 has a normally glycosylated IgG4-κ structure with an approximate molecular weight of 150.000 Daltons. It is assumed that TGN1412, like other antibodies, is catabolised by lysosomal enzymes in the kidney and/or liver into amino acids, which are then reabsorbed.

CD28 is expressed on most if not all CD4 T-cells and on a large fraction of CD8 T-cells. It is the most efficient receptor that co-stimulates resting T-cells in combination with the T-cell receptor (TCR). Activation of the CD28 signalling pathway naturally requires simultaneous triggering of the TCR by antigen and of CD28 by its physiological membrane-bound ligands B7-1 or B7-2. TeGenero's novel TGN1412 bypasses the requirement for TCR triggering and activates T-cells irrespective of their TCR specificity (see Figure 1). TGN1412 therefore represents the first universal T-cell growth factor applicable for therapeutic purpose in the intact organism.

TGN1412 has been generated to therapeutically balance the immune system in diseases associated with life-threatening abnormalities in T-lymphocyte number and/or function.

On the one hand, TGN1412 will be used to reconstitute a collapsed T-cell compartment in the context, e.g., of haemato-oncological malignancies such as B-cell chronic lymphocytic leukaemia (B-CLL). In ex-vivo experiments conducted with primary blood samples from a broad spectrum of B-CLL patients, it could be demonstrated that TGN1412 induces a profound polyclonal expansion and activation of T-lymphocytes as measured by absolute and relative T-cell counts and expression of activation markers such as CD25, CD69, CD40L and CD134 (Ox-40). On the tumour cell level, TGN1412 indirectly mediates up-regulation of CD80 and CD86 via the CD40/CD40L pathway. The improved antigen presentation by malignant B-cells is expected to result in an efficient recognition and elimination of leukaemic B cells by tumour-specific T-cells.

Thus, there is pre-clinical evidence that TGN1412 has the potential to add a significant benefit to B-CLL patients by improvement of T-cell numbers and function as well as induction of a long-lasting anti-tumour T-cell response.

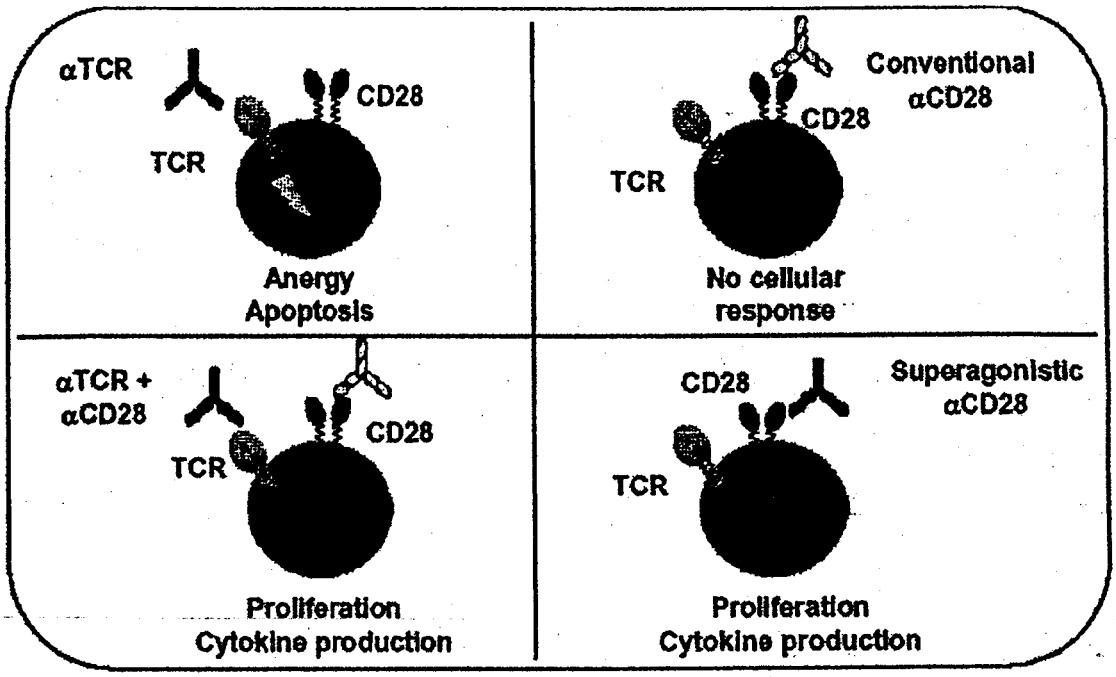

Figure 1: Mechanism of Action of TGN1412

TGN1412 bypasses the requirement for TCR signalling triggering and activates human T-cells irrespective of their TCR specificity. In T-cells, TCR triggering alone leads to anergy and apoptosis. Conventional anti-CD28 antibodies are not capable of inducing cellular T-cell response. Concomitant triggering via anti-TCR and anti-CD28 antibodies leads to proliferation and secretion of pro-inflammatory cytokines in vitro, but not in vivo. In contrast, TGN1412 induces profound in vitro T-cell proliferation and well tolerated in vivo expansion of T-cells.

On the other hand, TGN1412 has been shown in in-vivo animal models to be effective in the prophylaxis and treatment of autoimmune diseases such as rheumatoid arthritis (RA). There is pre-clinical evidence that TGN1412 interferes with pathomechanisms of autoimmune disease by induction of anti-inflammatory cytokines, inhibition of locally distributed pro-inflammatory cytokines and activation/expansion of the regulatory T cell compartment..

It is well established that auto-reactive T-cells contribute significantly to the pathogenesis of RA and that regulatory T-cells play a major role in the control of auto-reactive T-cells. TGN1412 has been shown to expand and activate regulatory T-cells in vitro and in vivo. Consequently, treatment of arthritic rats with a TGN1412 variant resulted in an efficient control of autoimmune disease symptoms.

Since the TGN1412 epitope appears to be restricted to humans and non-human primates, non-human primates (cynomolgus and rhesus monkeys) are considered the most relevant species to anticipate the safety and potential toxicity of TGN1412 in humans. A number of safety and efficacy studies with TGN1412 in non-human primates have been conducted using single- and multiple-dose regimens. The results of these

studies show that TGN1412 is well tolerated at doses up to 50 mg/kg for at least four consecutive weeks. No TGN1412-related signs of toxicity, hypersensitivity or generalized immunosuppression were observed in these studies. In a local tolerance study, intravenous (i.v.), perivenous (p.v.), or intraarterial (i.a.) routes of TGN1412 administration were well tolerated and did not produce clinically significant irritation.

Reproductive and developmental non-clinical toxicity studies were not yet performed. It is not known, whether TGN1412 can cause foetal harm when administered to a pregnant woman or affect reproductive capacity.

Non-clinical pharmacology studies have shown that TGN1412 has a predictable, well-defined pharmacokinetic profile following infusions of doses of 5 to 50 mg/kg. Thus, maximum serum concentration (C_{max}) and area under the curve (AUC) are largely proportional to dose and stable concentrations are observed with repeated dosing. TGN1412 is expected to have a consistent effect across different demographic groups and among patients with different diseases of varied severity.

For details of TGN1412 mode-of-action and pre-clinical data. Please refer to the TGN1412 Investigator's Brochure.

1.2. Outcome Measures

1.2.1. Safety

The primary objective of this first-in-man trial is to establish the safety and tolerability of TGN1412 in man by evaluation of ascending single doses of TGN1412. In addition, this trial will guide decision making for dose selection in subsequent studies.

The following tests are considered essential for evaluating the safety of this novel agent: adverse events (AEs), laboratory analyses including specific immunological methods, haematology, blood chemistry, urine analysis, vital signs, ECGs and physical examination. Evaluation of AEs will include assessments for injection site reactions.

It should be noted that the safety and tolerability of an immunomodulatory monoclonal antibody (albeit humanised), such as TGN1412, might not surface in the form of overt AEs or abnormal results from the standard battery of tests mentioned above. Indeed, a maximum tolerated dose (MTD) may not be identified on this basis but rather on basis of the effects of TGN1412 on the immune system. Thus, safety evaluations particular to TGN1412 will include the immunologic parameters:

- Number and phenotype analysis of lymphocyte subsets
- Serum levels of selected inflammatory cytokines
- C5a as a marker of complement activation
- Anti-TGN1412 antibody formation
- Epstein-Barr viral load
- Rheumatoid factor (RF), anti-nuclear antibodies (ANA)

A transient enlargement of lymph nodes was occasionally observed in pre-clinical studies at high doses in the cynomolgus monkey, which were most likely related to the pharmacology of the study drug. Therefore, palpable lymph nodes that may be observed during this study and, thus, they are to be closely monitored in this study.

In the case of an enlargement of peripheral lymph nodes that may be indicative e.g., for an excessive T-cell reaction, the Principal Investigator and/or the Data Safety Monitoring Board may decide to perform an abdominal ultrasound examination focussed on the spleen. If the spleen is enlarged, follow-up assessments may be performed at appropriate time points as judged by the clinician. In the case of an enlarged spleen size, follow-up examinations will have to show, whether this change is also of transient nature.

1.2.2. Pharmacokinetics

Single-dose pharmacokinetics (PK) analysis will enable a preliminary determination of the relationship between dose and serum concentration, and volume of distribution, clearance and half-life. Blood samples will be collected at regular intervals over the predicted time of TGN1412 systemic exposure (as determined from animal studies). The peak concentration of TGN1412 in the serum (C_{max}) and the time to reach peak concentration (t_{max}), overall systemic exposure (AUC_{0-t}, $AUC_{0-\infty}$), the apparent terminal elimination half life ($t_{1/2}$), volumes of distribution at steady state (V_{ss}) and associated with the terminal rate constant ($V_{\lambda z}$), total clearance (CL) and the mean residence time (MRT) will be determined.

The half-life of TGN1412 measured after single dose intravenous application may assist in determination of the dosing interval. Knowledge of the pharmacokinetic parameters for TGN1412 obtained from early trials will enable selection of doses for subsequent proof-of-concept /dose-ranging trials.

In case of generation of anti-TGN1412 antibodies, TGN1412 pharmacokinetics may be altered, for example by increasing or decreasing clearance. In this event, the impact of anti-TGN1412 antibodies on PK parameters should be carefully evaluated.

It is recognised, however, that the pharmacokinetic profile in patients with B-CLL or RA may differ from that in healthy subjects. The PK profile will also need to be evaluated in patients to determine comparability.

1.2.3. Pharmacodynamics

Pharmacodynamics (PD) measures used in the early phase clinical trials may provide information related to the dose-response relationship of TGN1412 and enable selection of the appropriate dose(s) for pivotal efficacy trials. The time course of PD activity may also be used to determine the most appropriate dose regimen. Although the PD dose-response relationship in healthy subjects may differ from that in patients due to a possibly altered expression number and/or activation state of T-lymphocytes and other critical activation/differentiation markers, it is likely that even in healthy subjects, agonistic triggering of CD28 will result in an effect on PD markers (such as T-lymphocyte subsets, cytokines and possibly immune status).

PD endpoints considered appropriate for this first-in-man trial include:

- The absolute and relative numbers of lymphocyte subsets
- The systemic cytokine release profile
- Ex-vivo assessment of T-cell function in response to mitogens or recall antigens

It is recognised that there may be a significant difference in the time course of PD activity, relative to systemic exposure, following TGN1412 administration. Alterations in the PK/PD profile may occur as a result of anti-TGN1412 antibody generation.

1.3. Study Rationale

To date, no human subjects have been exposed to TGN1412. The design and choice of trial population of this first-in-man (FIM) clinical phase-I trial is based on the need to initially demonstrate the safety of TGN1412 in man. The safety outcome measures in this trial, which may also answer questions concerning the mechanism of action of TGN1412, should help guiding the choice of dose and dose frequency for subsequent single- and multiple-dose studies in patients. In addition, serum drug concentrations will be measured to determine the rate and extend of escalating doses of TGN1412 in men.

Because so far no data on reproductive and developmental toxicity are available for this drug, it was decided to include male subjects in this FIM study only. Young women will be included in further studies once pre-clinical data are available. Studies in both genders of elderly subjects/patients will be performed once safety and tolerability have been shown in the young men included in the present study.

2. Study Objectives

2.1. Primary Objectives

- Assessment of the safety and tolerability of ascending single intravenous doses of TGN1412 in separate cohorts of healthy volunteers.
- Determination of the pharmacokinetics of single intravenous doses of TGN1412.

2.2. Secondary Objectives

- Determination the effect of administration of TGN1412 on lymphocyte subsets.
- Assessment of the cytokine profile following administration of TGN1412.
- Assessment of anti-TGN1412 antibodies up to 7 weeks post-dose.

3. Study Design

3.1. Description of Study Design

The study is designed as a single-centre, double-blind, randomised, placebo-controlled, dose-escalation trial, including 32 healthy male subjects, who will be divided into four groups of eight subjects each. In each group, six subjects will receive TGN1412 and two subjects placebo (random ratio: 3:1). Intravenous (i.v.) doses of 0.1, 0.5, 2.0 and 5.0 mg/kg body weight (b.w.) are planned to be investigated. These i.v. doses will be administered as short-term infusion. Dose escalation to the next dose level will proceed following satisfactory review of safety data from at least fourteen days following each administration. This review will be done by a Data Safety Monitoring Board. Dose escalation will take place only after the agreement of the sponsor and investigator.

Subjects will be screened for eligibility within 28 days from Day –28 to –2 before start of the experimental phase. Besides the assessment of the health state of the subjects, C-reactive protein (CRP) to exclude chronic inflammation will be determined. In addition, rheumatoid factor (RF) and anti-nuclear antibodies (ANA) will be assessed. Anti-TGN1412 antibodies will be measured and flow cytometry will be performed as well.

On Day –1, the subjects will be admitted to the Clinical Pharmacology Research Unit (CPRU) and stay there until Day 3. Further ambulatory visits are scheduled for Days 3 to 6, Days 8, 10, 12, 15, 18, 22, 29 and 36. The study drug will be administered in the morning of Day 1. Additionally, baseline levels for pharmacodynamic parameters as cytokines, blood samples for flow cytometry, immunoglobulins, RNA and *in-vitro* T-cell function will be collected at pre-dose. The final follow-up examination will be performed on Day 43, including also blood sampling for measuring of drug concentration and for assessment of all pharmacodynamic parameters.

Results of the analyses of cytokines in serum within 4 hours following single-dose administration of TGN1412 will determine the further time points of assessments. In case, an acute release of pro-inflammatory cytokines will be observed within 4 hours post-dose, all further samples for optional measurement will be examined.

In view of the possibility of anti-TGN1412 antibody formation, subjects will be followed for approximately seven weeks following TGN1412 administration.

3.2. Dose Rationale

A number of safety and efficacy studies with TGN1412 in non-human primates have been conducted using single- and multiple-dose regimen. The results of these studies showed that intravenous infusion (1-h infusion) of TGN1412 to cynomolgus monkeys at dose levels up to 50 mg/kg for at least four consecutive weeks were well tolerated. No TGN1412-related signs of toxicity, hypersensitivity or generalised immune system suppression were observed in these studies. Therefore, a dose level of 50 mg/kg body weight was considered the no-observed-adverse-effect level (NOAEL).

Based on a NOAEL of 50 mg/kg body weight, the clinical starting dose of 0.1 mg/kg body weight represents a 500-fold safety margin, which is considered sufficient by the company to ensure patient safety. The maximum dose in this clinical trial is 5.0 mg/kg body weight, still being 10-fold lower than the observed NOAEL in pre-clinical toxicology studies.

Pharmacological activity of agonistic anti-CD28 monoclonal antibodies has been determined in rodents and non-human primates at doses between 0.3 and 5.0 mg/kg body weight. Therefore, pharmacological activity of TGN1412 in humans may be expected in this dose range.

In this phase-I clinical trial, healthy volunteers will be treated on one of four dose levels of humanised agonistic anti-CD28 monoclonal antibody TGN1412 (0.1, 0.5, 2.0 and 5.0 mg/kg b.w.). Progression to the next dose cohort will be undertaken no earlier than 14 days after dosing of the previous cohort. Following evaluation of all available data from the previous cohort, a recommendation by a Data Safety Monitoring Board will be made for proceeding to the next higher level.

4. Study Population

4.1. Number of Subjects

A total of 32 eligible subjects will be included and are planned to complete this study, eight subjects in each dose group. Wherever possible, for each dose and each infusion group, two additional subjects will be included as backup in case of discontinuation of any subject. All subjects will be selected from a pool of subjects recruited by PAREXEL.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

To participate in this trial, subjects must meet all of the following criteria:

1. Healthy male, smoking or non-smoking subjects
2. Age between 18 and 40 years inclusive
3. Body mass index (BMI) between 18 and 28 kg/m^2 inclusive, with a body weight between 60 – 100 kg
4. Subjects are to be in good health as determined by a medical history, physical examination including vital signs, ECG recordings and clinical laboratory test results.
5. Normal CRP at screening and Day –1 to exclude chronic inflammatory processes
6. Subjects have to give their signed informed consent before any trial-related activity.

4.2.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from participation in the study:

1. Subjects with any infection or known inflammatory process elevated acute phase proteins (e.g., CRP)
2. Subjects with enlarged lymph nodes (e.g., head, neck, axillary, and inguinal)
3. In the opinion of the investigator, subjects with, or a history of cancer, diabetes or any clinically significant cardiovascular, respiratory, metabolic, renal (including renal stones), hepatic, gastrointestinal, haematological, dermatological, venereal, neurological, psychiatric or other major disorders
4. Subjects with a history of significant multiple drug allergies or with a known allergy to the trial product or any medicine chemically related to the trial product
5. Subjects who have any clinically significant allergic disease (including hayfever)
6. Subjects who have had a clinically significant illness within four weeks of dosing
7. Subjects with known serum hepatitis or who are carriers of the Hepatitis B surface antigen (HBsAg) or Hepatitis C antibodies or with a positive result to the test for HIV-1/2 antibodies
8. Subjects with clinically apparent hereditary or acquired immunodeficiency syndrome(s)

9. Subjects with acute gastrointestinal symptoms at the time of entering the trial (e.g., nausea, vomiting, diarrhoea, or heartburn)
10. Any clinically significant abnormal laboratory test results at screening, or any abnormal white cell count at screening and on Day –1
11. Subjects who have a supine blood pressure at screening, after resting for 5 min, higher than 150/90 mmHg or lower than 100/50 mmHg
12. Subjects who have a supine heart rate at screening, after resting for 5 min, outside the range of 40–90 beats/min
13. Subjects who have a clinically significant abnormal ECG at screening
14. Subjects who have received any prescribed systemic or topical medication within two weeks prior to screening
15. Subjects who have used any non-prescribed systemic or topical medication, except vitamins, within two weeks prior to dosing. Occasional use of paracetamol is permitted at the discretion of the investigator
16. Subjects who have received an investigational drug in four months (new chemical entity) or three months (licensed product) or subjects who received a vaccine within three months preceding the start of dosing
17. Subjects who have participated in this study on a previous dose level
18. Subjects who have donated any blood or plasma in the past month or in excess of 500 mL within the 12 weeks preceding screening
19. Subjects who have a significant history of alcoholism or drug/chemical abuse, or who have a positive result in the urine drug/alcohol screen, or who consume more than 28 units of alcohol per week (one unit of alcohol equals about 250 mL of beer or lager, one glass of wine, or 20 mL spirits)
20. Subjects with a significant use of caffeine-containing beverages (greater than eight cups per day)
21. Subjects with mental incapacity or language barriers which preclude adequate understanding or co-operation, who are unwilling to participate in the study, or who in the opinion of their general practitioner or the investigator should not participate in the study.
22. Subjects who have taken part in strenuous exercise within four days prior to dosing in this trial. During the trial, strenuous exercise is not allowed.
23. Subjects who had eaten poppy seed-containing food (e.g., poppy-seed cake) during the three days before the pre-study examination and three days prior to Day –1.

4.3. Stopping Criteria for the Subjects and for the Study

4.3.1. Withdrawal and Replacement of the Individual

Subjects will be withdrawn or may discontinue from the trial if the following will occur:

Subjects may discontinue treatment for the following reasons. The reason(s) will have to be recorded on the appropriate page of the Case Report Form (CRF):

1. The subject withdraws consent.

2. Development of an intolerable adverse event due to study participation as determined by the Investigator and/or subject
3. Development of an intercurrent illness, condition, or procedural complication, which would interfere with the subject's continued participation
4. Discovery that the subject entered the study in violation of the protocol or occurrence of a significant protocol violation during the study
5. The investigator feels it is medically in the best interest of the subject to discontinue the subject's participation in the study
6. Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risks to the subjects.

Subjects may be replaced after discussion between the sponsor and investigator. Subjects who discontinue will take part in a follow-up examination including a physical examination, vital signs, ECG and, if possible, safety laboratory tests including immunologic parameters. All subjects who drop out because of AE or clinical laboratory abnormality will be followed up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure reversibility or stabilization. The subsequent outcomes of these events will be recorded on the CRF.

4.3.2. Premature Termination of the Study

The study may be terminated prematurely if:

- The Principal Investigator and the sponsor feel that the number and/or severity of AEs justify discontinuation of the study.
- Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the Principal Investigator and the sponsor and must be documented. Study results have to be reported according to the requirements outlined in this protocol as far as applicable.

5. Investigational Product

5.1. Treatment Administered

Drug:	TGN1412	Placebo
Formulation:	Solution for infusion	Solution for infusion
Strength:	10 mg/mL	Not applicable
Manufacturer:	Boehringer Ingelheim AG, Biberach a. d. R., Germany	Boehringer Ingelheim AG, Biberach a. d. R., Germany
Batch number:	E5646LO04	E5653LO01
Expiry date:	09 July 2006	09 July 2006
Storing conditions:	5 ±3°C	5 ±3°C

For details of the treatment see the following sections.

5.1.1. Administration of the Study Medication

1. Preparation of the physiological NaCl-solution for TGN1412 or placebo dilution (all steps to be carried out under aseptic conditions in a laminar flow hood): plunge a Minispike through a septum wiped before with an ethanol-soaked pad into a bottle or directly into a bag also wiped before with an ethanol-soaked pad containing the sterile physiological NaCl-solution. Fit a 50 mL Perfusor-syringe via luer lock to the spike and draw syringe with 40 mL (160 mL total volume required). Disconnect syringe and Minispike leaving the Minispike in the septum. Fit syringe via Luer lock to the infusion bag provided for the dilution and release solution into it. Transfer 160 mL physiological NaCl-solution in total to the empty infusion bag, use one Minispike and one syringe for the complete transfer when sterility is warranted.

2. Diluting TGN1412 or placebo to prepare the solution to be perfused (all steps to be carried out under aseptic conditions in a laminar flow hood): fit a 50 mL Perfusor-syringe via Luer lock with a Minispike. Plunge through the septum of the TGN1412- or placebo-vial wiped before with an ethanol-soaked pad and draw syringe with 40 mL solution. Remove syringe, connect it via Luer lock to the infusion bag containing the physiological NaCl-solution (see 1.) and release solution into the infusion bag. Close Luer lock of infusion bag and invert it several times carefully to mix the components. Finally 40 mL original TGN1412 investigational medicinal product (10 mg TGN1412/mL) or placebo are mixed with 160 mL physiological NaCl-solution yielding the injectable solution with a concentration of 2 mg TGN1412/mL or without TGN1412 in case of placebo-use. The prepared solution is to be used within 6 hours.

3. Preparation of perfusion: Connect 50 mL Perfusor-syringe to the infusion bag via Luer lock and draw 50 mL injectable solution (see 2.) from the infusion bag (regardless of the actually required volume for the intended dose). Remove filled Perfusor-syringe from the

infusion bag and proceed to 4. if not more than 50 mL diluted TGN1412-solution ready for use are needed.
In case more than 50 mL are required for a single dose, two more 50 mL volumes and one 40 mL volume of the diluted TGN1412-solution ready for perfusion can be drawn from the same infusion bag for one volunteer. For each drawing a new Perfusor-syringe has to be used.
If more than 380 mg TGN1412 corresponding to 190 mL solution ready for use are to be perfused for a single dose, prepare a new 200 mL volume diluted TGN1412-solution in a new infusion bag as described in 1. and 2. Complete the required volume in 50 mL- and 40 mL-steps as just described.

4. Perfusion: determine the total amount of TGN1412 that is to be perfused for each volunteer dependent on body weight and the dosing group. In case of placebo administration calculate the total volume of diluted placebo-solution that is to be perfused for each volunteer dependent on body weight and the dosing group as if TGN1412 was present in the prepared placebo-solution.
Insert the Perfusor-syringe into the Perfusor, and then connect the Perfusor-syringe to the Perfusor-tube via Luer lock. Deaerate the system. Fit the free end of the Perfusor-tube via Luer lock to an indwelling cannula inserted in the volunteer's arm vein. In case more than 50 mL must be perfused for a single dose, a second, third etc. 50 mL-Perfusor-syringe (see 3.) must be inserted into the Perfusor. The Perfusor-tube remains connected to the indwelling cannula; prevent the Perfusor-tube from running dry.

Adjust speed of perfusion according to the TGN1412-dose (in mgTGN1412/kg bodyweight) as stated in the protocol. Correspondingly adjust speed of placebo-perfusion according to the TGN1412-dose to be placebo-controlled as stated in the protocol. For doses of 0.1 mg/kg and 0.5 mg/kg select a perfusion rate of 1 mL/min, for doses of 2 mg/kg and 5 mg/kg select 5 mL/min.
The total time for perfusion is individualised for each volunteer dependent on the total amount of TGN1412 or on the calculated volume of placebo-dilution to be perfused and on the selected perfusion rate.

5.1.2. Description

TGN1412 is a humanised monoclonal antibody directed against the human CD28 antigen. The molecule was genetically engineered by transfer of the CDR-regions from heavy and light chain variable gene fragments of a monoclonal mouse anti-human CD28 antibody (see Investigator's Brochure) into human heavy and light chain variable region frameworks. Humanised variable region genes were subsequently recombined with a human gene coding for the IgG4-γ chain and with a human gene coding for a human κ-chain gene, respectively.

Withheld under section 43(2) of the FOI Act - see page 4.

5.1.3. Formulation

Withheld under section 43(2) of the FOI Act - see page 4.

5.1.4. Manufacturer

Withheld under section 43(2) of the FOI Act - see page 4

5.1.5. Storing Conditions

Withheld under section 43(2) of the FOI Act - see page 4.

5.2. Drug Accountability

A drug inventory/dispensing record will be maintained and updated for all drugs withdrawn and dispensed. At the end of the study, one copy of the drug inventory/ dispensing record will be sent to the sponsor and one kept in the investigators' study file. The investigators are responsible for all drug supplies. Written documentation is mandatory. After completion of the study, all unused materials will be returned to the sponsor, unless otherwise requested by the sponsor in writing.

5.3. Supply and Return

All medication will be provided by Boehringer Ingelheim AG, Biberach a.d.R., Germany, on behalf of TeGenero AG, Würzburg, Germany, to the Parexel CPRU, London, UK, together with the certificates of analysis. A sufficient amount of spare medication will be provided as well. Parexel CPRU must complete and return the Drug Supply Confirmation to the sponsor. The pharmacy will also be responsible for the correct assignment of each subject.

Upon receiving the medication, the investigator or his personnel will dispense the medication only to the identified subjects of this study, following the procedures described in this study protocol and documented in the appropriate CRFs.

5.4. Packaging and Labelling

All packaging and labelling operations will be performed according to GMP and GCP rules. The study drugs will be labelled by the Parexel CPRU with the following information in English:

• **Study No:**	• 68419
• **Protocol No:**	• TGN1412-HV
• **EudraCT No:**	• 2005-003371-21
• **Batch No.**	• ###
• **Random No:**	• ###
• **Study day:**	• ###
• **Period**	• -
• **Drug**	• TGN1412
• **Content**	• ## mg TGN1412 in ## ml
• **Route of administration**	• Solution for intravenous infusion, dose according to the protocol
• **Expiry date**	• ######
• **Storage**	• Between 2-8°C
[redacted]	*see page 1
• **CRO**	• PAREXEL International Ltd, PAREXEL Clinical Pharmacology Research Unit, Floor 7, Northwick Park Hospital, Harrow HA1 3UJ.
• **Sponsor**	• TeGenero AG, Friedrich-Bergius-Ring 15, Würzburg, 97076, Germany.

Keep away from children
FOR CLINICAL TRIAL USE ONLY

This information, which is also labelled on the bottles for each subject, will be removed and transferred to the Case Report Form (CRF).

5.5. Blinding and Breaking the Blind

This is a double-blind study. The reference code will be provided by PAREXEL International GmbH, Department of Biometrics and Data Management, to Parexel CPRU. Parexel CPRU will reference the randomisation code to determine the medication to be dispensed for each subject. This will be dispensed into a suitably labelled container. Persons involved in this study, i.e. physicians/ nurses, participants as well as the Data Safety Monitoring Board, will remain blinded at all times, unless in the case of an emergency. In order to maintain the blinding, results from PK and PD assessments will only be passed to PAREXEL and the Data Safety Monitoring Board in a blinded manner.

One set of code break envelopes will be provided by PAREXEL International GmbH, Data Management and Biostatistical Services Department to the Parexel CPRU prior to dosing. These will contain the randomisation numbers and treatment allocation and are for use in emergency situations only.

The bioanalytical laboratory may be unblinded before database lock. No unblinded data will be reported before database lock.

5.6. Treatment Assignment

Each subject in each treatment group will be randomly assigned to receive active drug or placebo. Dropouts may be replaced after discussion between the sponsor and investigator.

Randomisation will be performed at PAREXEL International GmbH, Dept. of Biometrics and Data Management. During the trial the volunteers will be identified by ascending 3-digit random numbers, replacement numbers will start with 1XX, i.e. 118 instead of 018 as described in Table 1. The randomisation number will be written on the Case Report Forms (CRFs).

Table 1: Treatment Assignment

Dose	Randomisation number	Replacement numbers
0.1 mg/kg b.w.	001–008	101–108
0.5 mg/kg b.w.	011–018	111–118
2.0 mg/kg b.w.	021–028	121–128
5.0 mg/kg b.w.	031–038	131–138

Randomisation will be done in blocks of four subjects per dose level to ensure that the ratio 3:1 for active/placebo treatment may be applied.

5.7. Assessment of Compliance

All medication will be administered intravenously by the study physician. Thus treatment compliance could be regarded as being ensured in each subject. In addition, for those subjects who received active drug, serum concentrations may also serve as compliance control.

6. Study Assessments and Procedures

6.1. Time and Events Table

For the time and events table see Appendix A of this protocol.

6.2. Study Assessments

6.2.1. Screening

Within four weeks before dosing, the subjects will undergo two screening visits to check their eligibility based on the inclusion/exclusion criteria.

For the first screening visit, to be carried out between Days –28 and –2 the latest, the subjects will arrive at the CPRU after a 10-hour fast. The following assessments and procedures will be done:

- Signing of the Informed Consent Form
- Physical examination (with special attention to lymph nodes)
- Demographic data
- Medical history
- Previous and concomitant medication
- Vital signs (blood pressure, body temperature)
- Determination of CRP-level
- Determination of RF and ANA
- 12-lead ECG
- Safety lab (haematology, clinical chemistry, and urinalysis)
- Serology
- Drug screen

If considered eligible, based on the above-mentioned criteria, screening procedures will be continued on the second screening day between Day –12 and Day –5, in order to obtain the following specific information related to TGN1412 dosing:

- Determination of anti-TGN1412 antibodies
- Flow cytometry
- Complement C5a

If found eligible for the study in the judgement of the Investigator, the subjects will be asked to return to the CPRU in the morning of Day –1 for the experimental part. Subjects who failed screening will be recorded on a screen failure log showing reason for failure.

6.2.2. Experimental Phase

On all days of the experimental part and until follow-up, AEs and concomitant medication will be documented. All blood samples will be taken at pre-dose or at pre-dose time, if not annotated otherwise (i.e., PK and PD samplings).

Day –1

The subjects will report to the CPRU at about 07:00 in the morning. Additionally, a drug screen and urinalysis will be performed, blood samples taken for the determination of haematology, clinical chemistry, CRP, rheumatoid factor and ANA antibodies, and the subjects weighted for calculation and preparation of the individual dose of study medication.

Week 1: Day 1, Pre-Dose

Before dosing in the morning of Day 1, the following assessments and determination will be performed:

- Vital signs (blood pressure, body temperature)
- 12-lead ECG
- Blood samples for the determination of Epstein-Barr Virus-load (EBV-load), total interleukin 8 (IL-8) and complement C5a (+ optional complement factors)
- Baseline sample for PK (TGN1412 concentration)
- Blood samples for PD: flow cytometry, cytokines, immunoglobulin, RNA sampling (FoxP3, etc) and in-vitro cell function

Administration of the Study Drug

The study drug will be administered intravenously between 08:00h – 10:00h in the morning.

Week 1: Day 1, Post-Dose

After administration of the study drug, the following assessment and procedures will be performed:

- Vital signs at 0.5, 1, 2, 4, 8 and 12 hours after start of the infusion
- 12-lead ECG at 0.5, 1, 2, 4, 8 and 12 hours after start of the infusion
- Body temperature, at 1, 2, 4, 8 and 12 hours after start of the infusion
- Blood sampling for total IL-8 at 1 hour (optional) and 4 hours post-dose
- Blood sampling for PK: 1, 2, 4, 8 and 12 hours after start of infusionBlood sampling for PD: cytokines 1 hour (optional) and 4 hours post-dose

Week 1: Day 2

Withheld under section 43(2) of the FOI Act - see page 4

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Week 1: Days 3, 4, and 6

*

Week 1: Day 5

In the morning of Day 5, the following procedures and assessments will be performed:

*

Week 2: Day 8

Subjects will attend to the CPRU in the morning of Day 8, when the following assessments and procedures will be performed.

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* withheld under section 43(2) of the FOI Act - see page 4.

Week 2: **Days 10 and 12**

*

Week 3: **Days 15 and 18**

*

Week 4: **Day 22**

*

Week 5: **Day 29**

*

* Withheld under Section 43 (2) of the FOI Act - see page 4.

Week 6: Day 36

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6.2.3. Follow-up

*

* withheld under section 43(2) of the FOI Act - see page 4.

6.3. Restrictions

6.3.1. Dietary Restrictions and Fluid Restrictions

During their in-house stay, the subjects will be served standardised meals. From 22:00 in the evening of Day –1 until 4 hours after start of infusion on Day 1, the subjects will fasten until lunch will be served at 4 h post-dose. Fluids will be allowed ad libitum.

On all other days, the subjects will take their meals at customary times.

6.3.2. Concomitant Medication

All concomitant medications taken during the study will be recorded in the CRF. The Investigator (or designated study physician) must be informed as soon as possible

about any medication taken from the time of screening until the end of the clinical phase of the study (follow-up visit).

Paracetamol will be allowed if deemed appropriate in the opinion of the investigator . Its administration will be recorded in the CRF.

Although not to be expected after TGN1412 administration, a 'cytokine burst' or anaphylactic reactions theoretically could occur within the first few hours after infusion. In this case, high-dose glucocorticoids, anti-histaminic drugs as well as other appropriate treatment may be considered for symptom relief, as appropriate.

6.3.3. Other Restrictions

Sauna, sunbathing and strenuous physical exercise (including competitive sport) is not allowed from 72 hours before screening and prior to dosing until the End-of-study examination.

Subjects are not allowed to smoke during the confinement period.

Subjects should abstain from unprotected sexual intercourse for at least 3 months after the last dose of study medication was administered.

6.4. Methods

6.4.1. Administration of the Study Medication

The study medication will be administered by i.v. infusion, as generally outlined in Section 5.1. The blinded study drug will be prepared for each individual by a pharmacist under the supervision of the principal investigator. Infusions will be done using a Perfusor compact, B. Braun, Melsungen, Germany. All study drug will be administered from a Perfusor syringe (OPS), B. Braun, Melsungen, Germany. The infusion set will be purchased from B. Braun, Melsungen, Germany.

6.4.2. Clinical Assessments

6.4.2.1. Demographic Information

The following demographic data will be recorded for all subjects:

- Date of birth
- Sex
- Ethnic origin (Caucasian, African, Asian, other)
- Height, without shoes
- Body weight, without outer garments
- BMI
- Smoking and drinking habits

6.4.2.2. Medical History

The medical history comprises:

- Previous illnesses and medication

- Family history of immunological diseases
- diseases; auto-immunological diseases in parents or siblings
- History of drug and alcohol abuse
- Special history about any allergic disposition

6.4.2.3. Physical Examination

A physical examination within the following body systems will be performed:

- Eyes, ears, nose, throat, neck
- Respiratory system
- Central and peripheral nervous system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Musculoskeletal system
- Skin
- Lymph node palpation (head, neck, axillary, inguinal)
- Other appropriate system

Ultrasound of Spleen and Lymph Nodes

Ultrasound examinations will be done by an external specialist, using an appropriate ultrasound device, if required in the opinion of the principal investigator by the results of palpation examinations.

6.4.2.4. Vital Signs

Recording of vital signs comprises:

- Pulse (beats per minute), supine after 5 minutes rest
- Blood pressure (mmHg), supine after 5 minutes rest
- Oral body temperature (°C)

Blood pressure (systolic and diastolic) and pulse rate will be measured by means of an automatic blood pressure measuring device (DINAMAP ProCare™ 100, GE Medical Systems, Freiburg, Germany) after the subject has been in a supine position for at least five minute first. The same arm will be used for all measurements. The arm (right or left) used for measurements will be recorded in the CRF.

Oral body temperature will be measured for at least one minute by means of a Welsh Allyn Suretemp-100.

6.4.2.5. Twelve-lead Electrocardiogram (ECG)

A 12-lead resting electrocardiogram (ECG) with one-minute rhythm strip will be recorded at screening, and at the following visits 12-lead ECG is recorded (25 mm/s) on 10-second rhythm strip (or until at least including three evaluable ECG intervals) at the time points specified. During the clinical phase of the trial, the ECG recordings will be evaluated by the Investigator and by use of electronic measurements.

Parameters of particular interest are PR, QRS duration, QT intervals and RR. QTc interval measurements are evaluated according to the categories defined in the CPMP Guide for the assessment of potential QT interval prolongation. In addition QT dispersion, any changes in T-wave morphology and appearance of U-wave will be evaluated. The handling and evaluation of the ECGs will be done in accordance with the CPMP Points to Consider and detailed in a separate document.

The ECG will be recorded while the subject is resting in a supine position for at least 5 min. Lead placement will follow the SOP of Parexel CPRU.

The CORINA Marquette Cardiosoft™ software version 4.2 (GE Medical Systems, Freiburg, Germany) will be used to assess the parameters HR, RR, PQ/PR, QRS, QT and QTc. Additionally, the occurrence of de- or repolarisation disorders, arrhythmic disorders or other abnormalities will be assessed and obvious changes of ECG parameters compared with the pre-medication record will be commented.

A control of the automatic analysis will be performed by an experienced physician. If a manual reassessment is required, e.g. for QTc calculation, the mean from three consecutive RR-intervals will be calculated.

6.4.2.6. Laboratory Assessments

The safety laboratory parameters planned in the present clinical study include serology, haematology and clinical chemistry as well as urinalysis and urine drug screening (determined by TDL, London) using validated standard methods.

For **haematology**, a blood volume of 2 mL will be taken using polypropylene tubes containing 15 % potassium-EDTA for full blood cell count. For **clinical chemistry**, blood samples will be collected into an 8.5 mL SST vacutainer. The blood will be centrifuged and the obtained serum will be transferred into polypropylene tubes. At screening, the determination of hepatitis B surface-antigen (HBsAg), hepatitis C virus antibodies (HCV), and HIV-1/2 antibodies will be determined from the same sample. A separate 4.5mL Sodium Citrate vacutainer will be collected for the analysis of fibrinogen, PT & calculation of the INR ratio.

Urinalysis will be performed at TDL, London from a sample of mid-stream urine.

Alcohol/drugs of abuse screen: At least 5 mL fresh mid-stream urine will be screened.

The following laboratory parameters will be assessed:

Haematology	**Clinical Chemistry**
Haemoglobin	Sodium
Haematocrit	Potassium
Red blood cell count (RBC)	Calcium
White blood cell count (WBC)	Phosphate
Mean cell volume (MCV)	Creatinine
Mean cell haemoglobin concentration (MCHC)	Urea
	Uric acid
Platelet count	Glucose
Differential white blood cell count	Albumin
	Total bilirubin

Serology
Hepatitis B surface antigen (HBsAg)
Hepatitis C antibodies
HIV-1/2 antibodies

Immunological parameters
EBV-viral load
Total IL-8
Complement (C5+ optional)
Rheumatoid factor
ANA antibodies
Immunoglobulin levels

Alcohol/drugs of abuse screen (urine)
Alcohol (ethanol)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine
Methadone
Opiates

Alkaline phosphatase
Gamma-glutamyl transpeptidase (GGT)
Aspartate aminotransferase (AST, GOT)
Alanine aminotransferase (ALT, GPT)
C-reactive protein
Fibrinogen
Prothrombin time (INR and %)
Cholesterol (total)
Triglycerides
Creatinine kinase (CK)

Urinalysis
Protein
Glucose
Blood
Leucocytes
Specific gravity
pH
Ketones
Microscopic examination (sediment)

Immunological Safety Parameters

Blood sampling for the immunological parameters will be carried out: with the tubes named as follows:

EBV-viral load Total IL-8 Complement (C5+ optional)	6 mL K-EDTA Vacutainer
Immunoglobulin levels	3 mL non-additive vacutainer
Rheumatoid factor ANA antibodies	5 mL SST Vacutainer

For determination of EBV-viral load, complement, rheumatoid factor and ANA antibodies, the blood will be centrifuged and the obtained serum or plasma will be transferred into polypropylene tubes. These analyses will be performed at [redacted] using validated standard methods. For total IL-8, the cell-lyse-solution will be added to the blood sample in the ratio of 1:1, the mixture will be thoroughly shaken and incubated at room temperature for 2 – 5 min. Before measuring with an IL-8 test, the solution will be again shortly mixed. A centrifugation is not necessary.

see page 12

6.4.3. Adverse Event Monitoring

The condition of each subject will be monitored throughout the study. In addition, any signs or symptoms will be observed and elicited by asking the open question:

"How have you been feeling since you were last asked?"

The adverse events will be assessed and reported according to PAREXEL's International SOP.

6.4.4. Pharmacokinetics

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6.4.5. Anti-TGN1412 Antibodies

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6.4.6. Flow Cytometry

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* withheld under section 43(2) of the FOI Act - see page 4.

*

6.4.7. Cytokines

*

* Withheld under section 43(2) of the FOI Act - see page 4.

6.4.8. In Vitro T-Cell Function

*

6.4.9. RNA Analysis

*

* withheld under section 43 (2) of the FOI Act - see page 4.

6.4.10. Total Blood Amount

*

6.5. Treatment and Medical Care After End of the Study

No further treatment of the healthy subjects is planned after discharge out of this study.

* withheld under section 43(2) of the FOI Act - see page 4.

7. Adverse Events (AE) and Serious Adverse Events (SAE)

7.1. Definition of an AE

An adverse event (AE) is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment".

Adverse events include:

- Worsening (change in nature, severity or frequency) of conditions preset at the onset of the trial
- Patient / subject deterioration due to the primary illness
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.2. Definition of a SAE

During clinical investigations, adverse events may occur which, if suspected to be drug-related (adverse drug reactions), must be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function.

A serious adverse event (experience) or reaction is: "any untoward medical occurrence that at any dose":

- Results in death
- Is life-threatening*
- Is permanently disabling
- Results in patient / subject hospitalisation or prolonged hospitalisation
- Results in a congenital anomaly
- Results in a cancer (if not a cancer study)
- Results in overdose
- Other (medically significant, requiring intervention)

* NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

7.3. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to TeGenero AG in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by TeGenero AG. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to TeGenero AG.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

7.4. Evaluating AEs and SAEs

7.4.1. Relationship to Study Drug

Definite*

A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.

Probable*

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the subject / patient's clinical state.

Possible*

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could readily be produced by a number of other factors.

Unlikely

A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject / patient's clinical state.

Not related

Any event that does not meet the above criteria.

Unknown*

(*) When an adverse event has been assessed and causal relation to the study drug established or is unknown, it must be referred to as an adverse drug reaction.

7.4.2. Grading of Adverse Events

Mild: Causing no limitation of usual activities; the subject may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject / patient may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject / patient may experience intolerable discomfort or pain.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section "Definition of an SAE".

7.5. Reporting Serious Adverse Events

7.5.1. Reporting of SAEs to TeGenero AG

7.5.1.1. Timeframe for Submitting SAE reports to ~~TeGenero AG~~

SAEs will be reported promptly to TeGenero AG as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

Table 3: Timeframes for Submitting SAE Reports to TeGenero AG

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	"SAE" CRF pages	24 hours	Updated "SAE" CRF pages

Contact person at the Sponsor, the SAE reports are to be send:

[redacted]

Name(s) withheld under sections 40 and 38 of the FOIA – see page 1.

7.5.1.2. Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to TeGenero within 24 hours as outlined in Section "Reporting of SAE to TeGenero AG". The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to TeGenero within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying TeGenero AG of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section "Relationship to Study Drug".

Facsimile transmission of the "SAE" CRF is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the "SAE" CRF sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF within the time frames outlined in Section "Reporting of SAE to TeGenero".

All serious AEs will be reported to TeGenero AG within 24 hours. Facsimile transmission is always the preferred method of reporting (including non-working hours) to: [redacted] will ensure that information on all recent SAEs will be available to all other members of the Data Safety Monitoring Board. [redacted] as member of the Data Safety Monitoring Board will ensure the timely availability of written reports to all external members.

* information withheld under Sections 40 and 36 of the FOIA - see page 1.

7.5.2. Regulatory Reporting Requirements for SAEs

The investigator will promptly report all SAEs to TeGenero in accordance with the procedures detailed in Section "Reporting of SAE to TeGenero." TeGenero has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Independent Ethics Committee (IEC).

7.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to TeGenero on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that

follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

TeGenero may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, TeGenero will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed "SAE" CRF, with all changes signed and dated by the investigator. The updated SAE CRF should be resent to TeGenero within the time frames outlined in Section "Reporting of SAE to Sponsor".

7.7. Clinical Laboratory Evaluations

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the investigator as clinically significant, will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section "Definition of an AE", or SAE, as defined in Section "Definition of a SAE". Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8. Documentation of Data

8.1. Hard Copies of Case Report Forms

All data obtained in this study are raw data. PAREXEL staff members will record the data on CRFs immediately, except for data that are available on original printouts or as data files. If any forms of printouts are available, each copy of the printouts will be attached to each copy of the subjects' CRF folder.

It is the responsibility of the investigator to ensure that the CRFs are kept in order and up-to-date so that they always contain the latest observations on the subjects enrolled. Corrections must be made with a black ball pen. The entry to be corrected has to be crossed out but must remain legible. The correction then has to be made right next to the entry and confirmed by date, signature and reason, if applicable. Corrections, which cannot be made in this fashion, have to be explained in detail in a statement, reference to which has to be documented on the respective CRF.

CRFs must be completed legibly for each subject enrolled and signed by the investigator. This should be done as soon as possible after completion of the study. A monitor will review the CRFs.

All clinical work conducted under this protocol is subject to Good Clinical Practice rules. This includes an inspection by the sponsor and/or health authority representatives at any time. The investigator will agree to the inspection of study-related records by health authority representatives and/or the sponsor or third parties, named by the sponsor.

8.2. Data Entry in Database

All data documented on hard copies or printouts will be entered by PAREXEL using an independent double data entry system. This system provides an overwrite technique (blinded for the previous entry) and requires final conclusive entry in the case of a discrepancy; the system documents in an audit file all changes made to the data.

8.3. Check of Queries

The raw data will be checked with appropriate programs for consistency and plausibility according to previously defined query check ranges. Query sheets will be provided together with the raw data to the study physician for comments. Corrections due to these comments will be documented in the Data Management file.

8.4. Coding of Adverse Events, Drugs and Diseases

After data entry the AEs will be coded according to MedDRA, Version 7.0. Concomitant medication will be coded according to WHO Drug Reference List. Concomitant diseases will be coded according to 'Anatomical Therapeutic Chemical Classification System' (ATC).

9. STATISTICAL AND ANALYTICAL PLAN

All individual data will be listed as measured. All statistical summaries and analyses will be performed by PAREXEL International GmbH using SAS® (STATISTICAL ANALYSIS SYSTEM, SAS-Institute, Cary NC, USA). Statistical and analytical procedures will be detailed in a Statistical Analysis Plan (SAP).

Continuous measurements will be summarized by means of descriptive statistics (i.e. number of observations, mean, standard deviation, minimum, median, maximum). 95% confidence intervals may be given additionally.

Categorical data will be summarized by means of frequency tables (i.e. count and percentages).

Data of subjects having received placebo will be pooled in one group for analyses.

Statistical tests (ANCOVA) will be performed on a purely descriptive level. No adjustment for multiple testing will take place.

9.1. Sample Size

The total sample size of 32 subjects is not based on a formal statistical assessment. However, this number of subjects considered sufficient to achieve the objectives of the study. Each group will consist of eight subjects of whom six will receive active drug and two will receive placebo.

9.2. Pharmacokinetic Evaluation

The following pharmacokinetic parameters will be derived from serum concentrations of TGN1412:

C_{max}	Maximum TGN1412 concentration
T_{max}, t_{max}	Time to maximum TGN1412 concentration
AUC_{0-t}	Area under the TGN1412 concentration time curve in the interval from the first dose to last observed concentration value above lower limit of quantification
$AUC_{0-\infty}$	Area under the TGN1412 concentration time curve in the interval from the first dose to infinity (extrapolated after the last dose)
$T_{1/2}$, $t_{1/2}$	Terminal elimination half life
λ_z	Apparent terminal elimination rate constant
CL	Clearance
V_{ss}	Volume of distribution at steady state
$V_{\lambda z}$	Volume of distribution associated with the elimination rate
MRT	Mean residence time

Where applicable, PK parameters will be also be derived as 'normalised' by body weight.

Serum TGN1412 concentrations below the lower limit of quantification (LOQ) will be labelled as (BLQ) in the plasma TGN1412 concentration data listings and set to zero if recorded pre-dose and to 1/2 LOQ otherwise.

All TGN1412 profiles will be presented graphically as individual curves. In the first set, each graph shows the TGN1412 concentration versus time with clear indication of samples below the limit of quantification. In the second set, each graph shows the logarithm of the TGN1412 concentration versus time with a clear indication of samples below the limit of quantification. Both sets of curves will include subject identification and dose. Descriptive point-wise mean profiles will also be presented for all doses.

Selection of data points for calculation of λ_z will be based on inspection of log-concentration-time plots of individual profiles. For all subjects at least three of the last data points above the LOQ will be included in the calculation of λ_z. Calculation of AUC_{0-t} and $AUC_{0-\infty}$ will be conducted using the linear trapezoidal method.

The maximum serum concentration (C_{max}) and the corresponding time (t_{max}) will be read directly from the serum concentration-time data.

Pharmacokinetic characteristics will be summarized by the number of measurements, arithmetic mean, standard deviation, CV% (coefficient of variation in percent) minimum, median, maximum value and, in addition, by geometric mean and by dose group.

9.3. Pharmacodynamic Evaluation

Pharmacodynamic parameters will be summarised by descriptive statistics, by dose and study day. Changes from baseline will be summarised by descriptive statistics by dose.

Dose-response relationship will be explored on a descriptive level by means of an appropriate ANCOVA model with fixed factor 'treatment' and individual baseline measurements as covariate.

9.4. Safety Evaluation

9.4.1. Adverse Events

Adverse events will be summarised by dose, MedDRA 7.0, severity and relation to trial drug. The descriptive statistics presented for each system-organ class and preferred term will be the number of subjects with event (N), the percent of subjects exposed with event (%), and the number of events (E). All adverse events will be listed by subject, including demographic information, dose, MedDRA 7.0 system organ class and MedDRA 7.0 preferred term.

9.4.2. Clinical Laboratory

Clinical laboratory values will be summarised by descriptive statistics, by dose and study day. Changes from baseline in clinical laboratory will be summarised by descriptive statistics by dose. All clinical laboratory values outside normal range (including screening and post-trial) will be listed by dose and subject number and including demographic information and flagging of values.

9.4.3. Twelve-lead ECG

All ECG endpoints will be listed by dose, subject and time of assessment and summarised by descriptive statistics by dose. Changes from baseline in ECG parameters will be summarised by descriptive statistics by dose. Dose-response relationship will be analysed for the QTc endpoints by means of an appropriate ANCOVA model with fixed factor 'treatment' and individual baseline measurements as covariate. A drug concentration – QTc relationship will also be explored. Individual profiles of the ECG measurements and mean profiles per dose will be presented graphically.

9.4.4. Physical Examination

Subjects with any changes in the physical examination evaluation from baseline to End-of-Study visit will be listed. A description of the trial population in terms of baseline measures and demographics will be presented.

9.4.5. Immunological Parameters

Immunological values will be will be summarised by descriptive statistics by dose and study day. Changes from baseline immunological parameters will be summarised by descriptive statistics by dose.

9.5. Interim Analysis

No formal interim analysis will be performed. However, the investigator will prepare an interim clinical summary report of each dose level, including as a minimum all data from laboratory analyses outside normal range, all ECG and vital signs recordings (individual blood pressure and pulse curves, list of any borderline or prolonged QTc), and all adverse events reported following dosing, and the report will be reviewed by sponsor to allow progression to the next dose level. If there are no clinically significant changes, the study will proceed to the next higher planned dose level, as agreed upon by the investigator and representatives from sponsor.

10. REGULATORY AND ETHICAL ISSUES

10.1. General Legal References

The study will be carried out according to the Declaration of Helsinki, revised version of Edinburgh, 1996, and in accordance with local law and the requirements of Good Clinical Practice.

All clinical work conducted under this protocol is subject to Good Clinical Practice rules. This includes an inspection by the sponsor and/or health authority representatives at any time. The investigator must agree to the inspection of study-related records by health authority representatives and/or the sponsor.

10.2. Insurance

In accordance with Article 3 of Directive 2001/20/EC (The Protection of Clinical Trial Subjects), a clinical trial may be undertaken only if provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

10.3. Ethics Committee and Regulatory Authority

The final, approved protocol and the Informed Consent Forms will be reviewed by the responsible Ethics Committee (EC) and the national Regulatory Authority. The Committee's and Authority's decisions concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to TeGenero AG. The investigator agrees to submit any required progress reports to the Ethics Committee, as well as reports of SAEs, life-threatening problems or death to the EC and Regulatory Authority.

10.4. Protocol Adherence – Amendments

The protocol must be read thoroughly and the instructions must be followed exactly.

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and TeGenero AG. All the amendments have to be notified to the EC and the national Regulatory Authority.

Administrative changes, which have no significant impact on the medical or scientific validity of the study, will be documented in a statement. The EC may be notified of administrative changes.

10.5. Required Documents

The investigator must provide the sponsor with the following documents prior to the enrolment of any subject (copies should be kept by the investigator in the appropriate file folders provided):

- Signed copy (original) of the approved protocol
- Completed and signed statement of investigator
- Curriculum vitae of the investigator

- Copies of the votes from the Ethics Committee and the Regulatory Authority
- Sample of the written informed consent form to be used
- Name and location of the laboratories utilised for laboratory assays, and other facilities conducting tests, including laboratory certification number and date of certification if available
- List of normal laboratory values.

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided. The sponsor's monitor must be notified if the laboratory is changed.

10.6. Informed Consent

The subjects will give their informed consent prior to the pre-study screening examination.

Each subject's chart will have their signed Informed Consent Form for study participation attached to it. When the study treatment is completed, this Informed Consent Form will be kept in the investigator's central study folder. Study monitors and/or regulatory authorities may check the existence of the signed Informed Consent in this central study folder if not having done so during the performance of the trial.

10.7. Responsibilities

10.7.1. Responsibilities of the Sponsor:

- Select qualified investigators
- Provide each investigator with an up-to-date Investigator's Brochure or equivalent documents
- Provide the Principal Investigator with all information he/she needs for submission to the EC and Regulatory Authority or supports the investigator in this notification
- Provide fully characterised investigational medical product(s) prepared in accordance with GMP
- Inform investigator of any information of possible relevance to the clinical study that becomes available during a trial and ensure that investigator(s) (together with sponsor, when appropriate) notify the EC and/or regulatory Authority, where required.
- Provide adequate treatment/compensation for subjects in the event of injury; provide indemnity for the investigator.

10.7.2. Responsibilities of the Clinical Trial Monitors:

The monitors are the principal communication link between the sponsor and the investigator. In this study, monitoring will be performed by qualified monitors working independent from PAREXEL International, Clinical Pharmacology Research Unit, London. Responsibilities of the Clinical Trial Monitors include:

- Work according to predetermined SOPs, visit the investigator periodically to verify adherence to the protocol and assure that all data are correctly and completely recorded. In order to perform his/her role effectively, the monitor must be given

access to primary subject data which supports data on the CRF for the study, i.e. hospital and general practice charts, appointment books, original laboratory records, etc.

- Ensure that the trial site has adequate space, laboratory equipment, staff and that an adequate number of trial subjects is likely to be available for the duration of the trial
- Ensure that all staff assisting the investigator in the trial has been adequately informed about the details of the trial
- Ensure that Informed Consent has been obtained and recorded from all the subjects prior to their participation in the trial
- Provide for communication between the investigator and sponsor promptly and at any time
- Check that the storage, dispensing and documentation of study drug(s) are safe and handled in accordance with local regulations as well as study requirements
- Assist the investigator in any notification/application procedure
- Assist the investigator in reporting the trial data and results to the sponsor
- Submit to the sponsor a written monitoring report after each site visit and written documentation of all relevant telephone calls, letters and other investigator contacts.

10.7.3. Responsibilities of the Investigator

- Be thoroughly familiar with the properties of the study drug(s) as described in the Investigator's Brochure
- Ensure that he/she has sufficient time to conduct and complete the trial, has adequate staff and appropriate facilities and that other trials do not divert essential subjects or facilities away from the trial in hand
- Provide retrospective data on numbers of subjects who satisfied the proposed entrance criteria during preceding time periods, in order to assure an adequate recruitment rate for the trial
- Submit an up-to-date curriculum vitae and other credentials to the sponsor and where required to relevant authorities
- Agree and sign the protocol with the sponsor and confirm in writing that he/she will work according to the protocol and Good Clinical Practice accepting the role of the monitor and the need for control procedures
- Nominate (if appropriate) a local study coordinator or co-investigator(s) to assist in the administration of the trial
- Submit notification/application to the relevant authorities when appropriate
- Submit notification/application to relevant bodies including local hospital management and to EC jointly with the sponsor where appropriate
- Provide information to all staff members involved in the trial
- Fully inform trial subjects about the clinical trial and obtain their informed consent
- Certify that all study drug(s) have been correctly delivered, stored and safely handled, and that reconciliation of stock can be justified. Account must be given of any discrepancies. Certificates of delivery and return must be signed

- Manage drug randomisation code procedures and documentation with care
- Collect, record and report data properly
- Notify sponsor (and relevant authorities when required) immediately in the case of serious adverse events and take appropriate measures to safeguard subjects.
- Agree with and sign the Final Report of the trial
- Ensure that the confidentiality of all information about subjects is respected by all persons involved as well as the information supplied by the sponsor
- Make all data available to the sponsor/monitors or relevant authorities for validation/ audit/inspection purposes
- Provide subjects enrolled in the trial with a card bearing information that he/she is participating in a Clinical Trial. Contact addresses/telephone numbers should be provided
- Medical records should be clearly marked to show that the subject is participating in a Clinical Trial
- The signature and initials of all staff who are authorised to be involved with the study must be provided on the Study Personnel Form.
- Notify regulatory authorities within the required time frame in the case of serious adverse events.

10.8. Monitoring

The clinical monitor will monitor the study on behalf of the Sponsor. The purpose of these monitoring visits is to confirm the following:

1. The study is being conducted according to the protocol and within the specified time frame.
2. The data are being collected accurately and completely on the CRFs and source documents.
3. The study medication is being correctly prepared, dispensed, and accounted for.
4. Adverse events are being correctly reported.
5. The facilities and staff remain adequate.

In addition, the purpose of the monitoring visit is to retrieve completed CRFs.

10.9. Quality Assurance

In accordance with the ICH GCP Guidelines the Quality Assurance Unit of PAREXEL International GmbH, Berlin, Germany, will perform selective audits during the course of the study. The audits will include control of adherence to the protocol, SOPs, GCP Guidelines and national laws. Source data verification and checking of data entered in the CRFs will be used for assessment of complete and reliable documentation.

10.10. Record Retention

The source data will be kept in the archives of PAREXEL International, London, UK, for at least two years after the last approval of a marketing application. TeGenero AG will inform PAREXEL International GmbH, Berlin, Germany, about the approval or specify

the duration of record retention after approval has been obtained. The original CRFs will be sent to TeGenero AG.

All correspondence relating to this study should be kept in appropriate file folders. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g., sponsor, other investigator) who will accept the responsibility. Notice of this transfer must be made to and agreed upon by the sponsor.

10.11. Confidentiality

PAREXEL International, London, UK, and TeGenero AG affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of TeGenero AG; it shall not be disclosed to others without written consent of TeGenero AG and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by TeGenero AG as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the investigator is obliged to furnish TeGenero AG with the complete test results and all data compiled in this study.

10.12. Publications

The publication of any data generated during or after the conduct of this clinical trial requires the written allowance of TeGenero AG.

11. REFERENCES

Investigator's Brochure, TGN1412 Edition 1.1 19 Dec 2005

12. Investigator's Statement of Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by TeGenero AG.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Clinical Investigator's Brochure / Investigator's Brochure (CIB/IB) or equivalent document, CIB/IB supplement (if applicable), and approved product label (if the product is marketed in this country and the label is not already provided as an equivalent to a CIB/IB).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study-related duties and functions as described in the protocol.

[redacted]

21 DEC 2005
Date

* Name(s) withheld under sections 35 and 40 of the FOIA - see page 1.

NOTE: Time and Events Table (pages 59-60) withheld under section 43 (2) of the FOI Act - see page 4.