CLINICAL TRIAL
ASSESSMENT REPORT
PHARMACEUTICAL DATA

Eudract Number: 2005-003371-21

TGN 1412 is a new presentation of a new drug substance. The aim of the proposed clinical trial is to determine safety, pharmacokinetics, pharmacodynamics and immunogenicity. The maximum daily dose is 5 MILLIGRAMMES Total and the duration of exposure is 1 Day. A placebo will be used.

DRUG SUBSTANCE
GENERAL INFORMATION
Nomenclature
TGN1412 is recombinant humanized agonistic anti CD28 monoclonal antibody

General properties
An adequate description of glycosylation is included.

MANUFACTURE
Manufacturer(s)
The drug substance is manufactured by Boehringer Ingelheim Pharma GmbH & Co KG, 88397 Biberach/Riss, Germany.

Description of Manufacturing Process and Process Controls
An adequate summary of the manufacturing process and process controls is provided.

The purification process is a seven-step process.
It is adequately described.

It is assumed that no reprocessing is undertaken.

Control of Materials
Adequate information on the development genetics is provided. This includes information on the gene of interest, gene construction and rationale.

The producer strain/host cell is described. This is a CHO cell line.

The production of the MCB has been described along with a description of the testing undertaken. This is acceptable.

No plasma derived components are used during manufacture.

Cholesterol (sheep wool), nucleotides (salmon) and sodium NADP (chicken liver) are animal derived components used during manufacture. See A.1

Controls of Critical Steps and Intermediates
No information is provided for isolated intermediates. This is acceptable.

The manufacturing process has not been validated. This is acceptable.

The purification process has not been validated other than for viral clearance/inactivation. This is acceptable.

CHARACTERISATION
Elucidation of Structure and other Characteristics
Evidence of structure
Adequate evidence of structure has been provided. This has been demonstrated by peptide mapping, oligosaccharide mapping and biological activity. The preclinical testing was performed using material produced at the 80L scale. The clinical material is produced at 2000L scale. Comparability data (IEF, peptide mapping, oligosaccharide mapping, SDS-PAGE, SEC-HPLC and binding assay) have been provided.

Too few batches have been produced to show batch-to-batch consistency.

There is no native form of this protein.

Physico-Chemical Characteristics
Adequate details of this aspect are provided.

Impurities
Adequate information on potential process-related impurities has been provided. No discussion of product related impurities has been provided. Residual Protein A, HCP, DNA and IGF-1 are not controlled in the specification. The data available to date shows good clearance.

CONTROL OF DRUG SUBSTANCE
Specification
An adequate drug substance specification has been proposed.

Analytical Procedures
Test methods have been described and are satisfactory.

Validation of Analytical Procedures
A summary of the validation data generated for the analytical methods has been provided and is acceptable.

Batch Analyses
Batch analysis data have been provided for two batches manufactured in May 2005 at a batch size of 2000L. These show good compliance with the proposed specification.

Justification of Specification
No further justification of the proposed specification is required.

REFERENCE STANDARDS OR MATERIALS
Batch analysis data have been provided for the reference standard.

CONTAINER CLOSURE SYSTEM
Batches are stored in EVA Bio-Process bottles.

STABILITY
The results of long term (3 months at 5 degrees C) and accelerated stability studies (3 months at 25 degrees C) have been presented for one batch stored in EVA containers. Supporting 3 month real time and accelerated data are provided for one batch manufactured at the 80L scale. No significant change on storage was observed. The proposed retest period should be confirmed.

DRUG PRODUCT
The drug product is a concentrate for infusion containing 10mg/ml of TGN1412.

COMPOSITION (mg/ml)
The composition of the drug product has been provided. The excipients are sodium acetate, sodium chloride, Tween 20, acetic acid and WFI.

PHARMACEUTICAL DEVELOPMENT
A brief discussion of the pharmaceutical development is provided.

MANUFACTURE
Manufacturer
The drug product is manufactured by Boehringer Ingelheim Pharma GmbH & Co KG, 88397 Biberach/Riss, Germany. It is assumed that the QP releasing the product is named on the manufacturer's authorisation for Boehringer Ingelheim Pharma GmbH & Co KG.

Batch Formula
No manufacturing formula is provided.
Description of Manufacturing Process and Process Controls
The manufacturing process for the drug product has been described and is acceptable. This is a filling process. Sterilisation is by filtration (0.2um). Filters are integrity tested before and after use. Bioburden is controlled in the drug product specification.

Controls of Critical Steps and Intermediates
No intermediates are involved.

Process Validation and/or Evaluation
To date, no process validation has been undertaken. This is acceptable. The aseptic processing has been validated by media fill runs.

CONTROL OF EXCIPIENTS
Specifications
The excipients all comply with the requirements of the relevant Ph Eur monographs.

Excipients of Animal or Human Origin
No excipients are of animal or human origin.

Novel Excipients
Not applicable.

CONTROL OF DRUG PRODUCT
Specification
An adequate drug product specification has been proposed.

Analytical Procedures
Test methods have been described and are satisfactory.

Validation of Analytical Procedures
A summary of the validation data generated for the analytical methods has been provided and is acceptable.

Batch Analyses
Batch analysis data have been provided for one batch of drug product. This shows good compliance with the proposed specification.

Justification of Specification
No further justification of the proposed specification is required.

REFERENCE STANDARDS OR MATERIALS
As for the drug substance.

CONTAINER CLOSURE SYSTEM
The concentrate for infusion will be packed in Type I glass vials with Teflon coated rubber stoppers.

STABILITY
The results of long term (3 months at 4 degrees C) and accelerated stability studies (3 months at 25 degrees C and 2 months at 40 degrees C) have been presented for one batch stored in glass vials. Supporting 9 month real time and accelerated have been provided for 80L scale material. There was a decrease in purity under accelerated conditions but this was not observed under real time conditions. The data provided, although limited, tend to support the proposed shelf life of 13 months when stored at 2-8 degrees C. It is assumed that the Clinical Trials Unit will be advised of any unexpected findings in the on-going stability testing. Any extension of the shelf life of the drug product will require the prior submission and approval of a substantial amendment.

APPENDICES
A1. Adventitious Agents Safety Evaluation
1.1. Non-viral adventitious agents
Adequate data on non-viral adventitious agents has been provided.

The TSE status of the BSA used in the freezing medium has been addressed by an EDQM Certificate of Suitability (R0-CEP 2001-051-Rev00).

Testing for bacteria, fungi and mycoplasma is performed on the MCB and pre-harvest.

1.2. Adventitious viruses
Adequate data on adventitious viruses has been provided.

Testing of the MCB included testing for adventitious virus (in vitro and in vivo) and bovine viruses.

Viral validation studies have been undertaken using MuLV, REO-3 and PPV. The steps investigated were low pH, anion exchange chromatography, hydrophobic interaction chromatography and nanofiltration.

A2. Novel Excipients
Not applicable.

A3. Comparator Products
Placebo Comparator
A placebo comparator will be used.

Adequate information on the product has been provided.

A4. Labelling
A sample of the labelling has been provided. It is assumed that this is the labelling for the infusion following dilution. A sample of the vial label should be provided.

A5. Manufacturer's authorisation
A copy of the manufacturer's authorisation has been provided.

ASSESSOR'S OVERALL CONCLUSIONS
The data provided raise no major concerns regarding the quality of the product to be used in the proposed clinical trial. There are seven points for clarification which the applicant should address.

LIST OF QUESTIONS TO THE APPLICANT
* It is assumed that no reprocessing is undertaken during manufacture of the drug substance.
* A discussion of potential product related impurities should be provided.
* The proposed retest period for the drug substance should be confirmed.
* It is assumed that the QP releasing the product is named on the manufacturer's authorisation for Boehringer Ingelheim Pharma GmbH & Co KG.
* It is assumed that the Clinical Trials Unit will be advised of any unexpected findings in the on-going stability testing. Any extension of the shelf life of the drug product will require the prior submission and approval of a substantial amendment.
* A sample of the labelling has been provided. It is assumed that this is the labelling for the infusion following dilution. A sample of the vial label should be provided
* It is assumed that the diluent is a UK marketed product.

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* It is assumed that the Clinical Trials Unit will be advised of any unexpected findings in the on-going stability testing. Any extension of the shelf life of the drug product will require the prior submission and approval of a substantial amendment.
* A sample of the labeling has been provided. It is assumed that this is the labeling for the infusion following dilution. A sample of the vial label should be provided
* It is assumed that the diluent is a UK marketed product.

<GNA Remarks (remarks from Application Decision page with GNA outcome)>

PHARMACO-TOXICOLOGICAL (SAFETY) ASSESSMENT

EUDRACT NUMBER: 2005-003371-21
CTA NUMBER: 27431-0001-001-0001
PRODUCT: TGN 1412
SPONSOR: TeGenero AG
THERAPY: Pathogenesis of chronic inflammation or haematological malignancies such as leukaemia.

POSOLOGY: The investigational medicinal product (IMP), TGN1412, will be administered intravenously per infusion to the clinical trial subjects as four single doses, at 0.1, 0.5, 2.0 and 5.0 mg/kg body weight. 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.

TYPE OF TRIAL AND PHASE (SCOPE): Phase I, FTIM.

DESIGN OF TRIAL: A Phase I, single-centre, double-blind, randomised, placebo-controlled, single escalating-dose study to assess the safety, pharmacokinetics, pharmacodynamics and immunogenicity of TGN 1412 administered intravenously to healthy volunteers.

MAXIMUM DURATION OF TREATMENT: 1 day

MAXIMUM DOSE: 5 mg/kg - total

POPULATION OF TRIAL SUBJECTS: Healthy males, 18-40 years of age.
Subjects should abstain from unprotected sexual intercourse for at least 3 months after the last dose of study medication was administered.

NUMBER OF SUBJECTS (WW/EU/UK): 32/32/32

1. INTRODUCTION

The objective of this first-in-man study 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 primary endpoint of the study is to assess the safety and tolerability of ascending single intravenous doses of TGN1412 in separate cohorts of healthy volunteers and to determine the pharmacokinetics of single intravenous doses of TGN 1412.

TGN1412 is a humanized agonistic IgG4 antibody directed against the human CD28 antigen expressed on T lymphocytes (T cells). In addition to TGN1412, alternative agonistic anti-CD28 antibody formats have been used in pre-clinical pharmacodynamic studies. The most prominent antibody format for pre-clinical evaluation of agonistic anti-CD28 antibody mode-of action is the mouse-anti-rat CD28 monoclonal antibody JJ316 (Tacke et al, 1997). Alternatively to TGN1412, an IgG1 variant with an identical variable domain structure (TGN1112) has been used in pharmacology studies in rhesus monkeys and with human cells. Comparability of homologous agonistic anti-CD28 antibody formats has been demonstrated by antigen binding and functional assays.

2. PHARMACOLOGY

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 signaling 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. TGN1412 therefore represents the first universal T-cell growth factor applicable for therapeutic purpose in the intact organism.

3. SAFETY PHARMACOLOGY

Safety pharmacology comprises a number of categories of tests and procedures which are intended to provide an assessment of the pharmacological profile of a novel drug in areas other than the intended therapeutic use. Usually unintended effects on the central nervous system (CNS), cardiovascular system (CV) and respiratory system are investigated. Usually, two acute rodent safety pharmacology studies are required to assess potential change s of behavior and respiratory system. These studies cannot be conducted in non-human primates. Since TGN1412 is highly specific for primate CD28 (see section 4.5 .1), studies in rodents or dogs are not expected to deliver meaningful results. Due to the fact that no cross reactivity with cardiovascular tissue has been observed for TGN1412 [redacted], it is believed that a telemetry study in cynomolgus monkeys is not reasonable at this stage of development and that it is sufficient to evaluate safety pharmacology endpoints as part of toxicology and pharmacology studies.

FOIA 42(2)

Cardiovascular system (CV)
As described above, TGN1412 does not cross react with cynomolgus monkey or human heart tissue. In addition, no electrocardiogram changes (heart rate, P-R interval, QRS interval and Q-T interval) were observed in the main 28-day repeated dose toxicology study in cynomolgus monkeys. No toxicologically significant differences in histology findings were observed in cardiovascular tissues (aorta, heart) between control and treatment group animals. Therefore, it is concluded that treatment with TGN1412 is not expected to adversely affect the cardiovascular system.

Respiratory system (RS)
In cross reactivity studies with cynomolgus and human tissues it was observed that TGN1412 binds to lymphocytes in lung tissues, in accordance with the target antigen (CD28) distribution. Although no specific functional assessment of the respiratory system has been performed as part of the 28-day toxicology study, no clinical observations were made that would support an unintended effect of TGN1412 on the respiratory system. No treatment related necropsy and histology findings were reported for the respiratory system (trachea, lung). Therefore, it is concluded that treatment with TGN1412 is not expected to adversely affect the respiratory system.

Central nervous system (CNS)
Specific fibrillary staining with TGN1412, considered to represent astrocyte staining, was seen in the brain (cerebrum, cerebellum), spinal cord and pituitary gland of both human and cynomolgus monkey donors. This cross reactivity with CNS tissue may not be of major clinical relevance, since no CNS related observation were reported during toxicology studies, including the 28-day repeated dose

toxicology study in cynomolgus monkeys. In addition, no histology findings were observed in nervous tissues (eye, brain, optic nerve, sciatic nerve) that could be attributed to treatment with TGN1412. Therefore, it is concluded, that treatment with TGN1412 is not expected to adversely affect the central nervous system.

4. PHARMACOKINETICS

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 (Cmax) 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 protein-based biotechnology derived medicinal products, classical ADME studies are considered not to be required, because pathways of protein degradation are common knowledge. It is assumed that TGN1412, like other antibodies, is catabolized by lysosomal enzymes in the kidney and/or liver into amino acids, which are then reabsorbed. Thus, conventional distribution, metabolism and excretion studies are not intended to be performed for TGN1412.

In contrast to the majority of therapeutic antibodies, TGN1412 does not act directly on malignant or pathological cell/ tissue structures. Due to the mode of action of TGN1412, pharmacodynamic effects are not expected to be solely correlated to plasma/ serum concentrations of the active substance, but rather be dependent on the transient activation of T cells or certain T cell subsets in the peripheral blood and lymphoid tissues.

FOIA 43(2)

Serum/ plasma concentrations of surrogate agonistic anti-CD28 antibodies JJ316 and TGN1112 as well as the kinetics of T cell activation have been determined in arthritis prone rats [redacted] and in the rhesus monkey [redacted] It was observed that in rats, JJ316 mediated T-cell expansion and activation appears to be faster than in non-human primates treated with either TGN1112 or TGN1412, which is also reflected by a lower estimated half-life of the agonistic anti-CD28 antibody in rats. This difference is expected, as it mirrors the general diversity (genetic background, physiology) of rodents and non-human primates. Therefore, pharmacokinetic (toxicokinetic) characteristics of TGN1412 as determined in cynomolgus monkeys are assumed to be most predictive for human PK.

FOIA 43(2)

FOIA 43(2)

Toxicokinetics of TGN1412 was assessed in the course of the pilot toxicology study [redacted] and as part of the 28-day repeat-dose toxicology study performed in cynomolgus monkeys [redacted] TGN1412 serum concentration vs. time profiles were generally consistent with intravenous injection of a monoclonal antibody medicinal product. Since toxicokinetic profiles of treated animals were somewhat variable, mean values per dose group were calculated on the basis of bioanalytical results from the 28-day repeat dose toxicology study. A terminal elimination half-life of ~8 days after the first injection of 5 mg/kg was estimated for TGN1412 in cynomolgus monkeys. Systemic exposure to TGN1412 increased by up to 20-fold as doses increased from 5 to 50 mg/kg. In addition, there was evidence for increased mean terminal half-life of TGN1412 as the dose increased.

Due to its integration into toxicity testing and its bridging character between non-clinical and clinical studies, the focus of toxicokinetic studies was primarily on the interpretation of toxicity tests and not on characterising the basic pharmacokinetic parameters of the substance studied.

5. TOXICOLOGY

Binding of TGN1412 and TGN1112 to T cells of several primate species has been investigated. Both antibodies specifically react with human, rhesus and cynomolgus T cells but not with marmoset lymphocytes. TGN1412 does not cross-react with rat or mouse CD28.
The findings are supported by a homology analysis on the basis of the C"D loop amino acid sequence. A homology of 100% could be found when C"D loop sequences of human, cynomolgus and rhesus monkey origin were compared, whereas the marmoset C"D differs in 2 out of 6 amino-acids. The rodent C"D loop is characterised by a very low or no homology to human CD28 C"D loop. The C"D loop sequence of dog, cat and woodchuck exhibits two amino-acid mutations in the binding epitope. Consequently, homology studies indicate that TGN1412 is not expected to react with the CD28 molecule from species other than primates.

Single dose (acute) toxicity of a novel medicinal product should be evaluated in two mammalian species (usually two different rodent species) prior to the first human exposure (ICH-M3). Due to the specificity of TGN1412 for human and non-human CD28, a standard single dose toxicity testing in rodents was considered to appropriate.

A pilot study to assess safety, pharmacodynamics, pharmacokinetics and tolerability of TGN1412 (n=1) and the IgG1 variant TGN1112 (n=2) has been conducted in rhesus monkeys (macaca mulatta, [redacted]). Both antibodies bind rhesus lymphocytes ex vivo with comparable efficacy, however, TGN1112 showed superior ex vivo pharmacological T cell activating capacity and was therefore more closely examined.

FOIA 43(2)

TGN1412 or TGN1112 were injected i.v. at a total dose of 2.5 mg/kg or 5 mg/kg body weight. Routine health assessment of animals included palpation of lymph nodes (axial, inguinal, and abdominal), examination of heart, lungs and oral cavity. All treated animals tolerated TGN1412 or TGN1112 injection well. Haematological parameters (haemoglobin, haematocrit, erythrocyte counts and thrombocytes) were not affected by antibody treatment.

A 2-fold transient increase in CD4 and CD8 cell numbers peaking at day 16 was observed after TGN1112 treatment. Rhesus-anti-human antibodies (RAHA) were determined by ELISA. Only a moderate RAHA response was observed in treated animals, appearing around day 20. Both anti-isotype and anti-idiotype responses were observed in the animal treated with 5 mg/kg, whereas anti-isotype and anti-idiotype response in the animal treated with 2.5 mg/kg was very low.

It was observed that TGN1412 had a significant lower pharmacological activity in rhesus monkeys as compared to TGN1112. This may be explained by different affinities and/or FcR binding properties of the two antibody formats. For toxicology studies with TGN1412, the cynomolgus monkey was selected as the more appropriate non-human primate species. Various pilot repeat dose studies were performed, based on the results of these studies, doses of 0, 5 and 50 mg/kg (4 weekly injections) were selected for the pivotal 28 day study. The once weekly one-hour slow intravenous infusion of TGN1412 to cynomolgus monkeys at dose levels up to 50 mg/kg (the maximal practicable dose for this route of administration) for four weeks was not associated with any toxicologically significant changes and this dose level was therefore considered to be the no-observed-adverse-effect level (NOAEL) as identified in this study. Generally, the immunogenicity of TGN1412 was low in cynomolgus monkeys. Only four out of 16 treated animals showed substantial titres of anti-TGN1412 antibodies in serum. These were observed 3 to 4 weeks after start of dosing.

TGN1412 expanded CD4+ and CD8+ T cells efficiently in male animals at the 5 mg/kg dose level. Increase in CD25+CD4+ T cell numbers appeared to correlate with absolute CD4+ cell counts. There were less optimal responses observed in females and at the 50 mg/kg dose level. The observed changes in absolute T cell numbers are an expected pharmacodynamic response to TGN1412 treatment. There was no evidence for an unintended induction of substantial pro-inflammatory cytokine release or of autoimmune disease in animals treated with any agonistic anti-CD28

monoclonal antibody. Treatment of cynomolgus monkeys with TGN1412 resulted in transient and moderately elevated serum levels specifically of IL-2, the inflammatory cytokine IL-6 and the anti-inflammatory (TH2 type) cytokine IL-5. Increased secretion of these cytokines appeared to be dependent on the dose administered. IL-2 serum levels were only elevated in high dose group animals. Serum levels of two additional major pro-inflammatory cytokines, TNFα and IFNγ, were not substantially elevated after first dosing with TGN1412. Elevated cytokine levels in individual animals did not correlate with increased numbers of (activated) T cells or other leukocyte subsets.

Local tolerance was assessed as part of the toxicology studies in cynomolgus monkeys (intravenous route of administration) and rabbits (intravenous, perivenous and intra-arterial route of administration). Minor local reactions at the injection sites of treated cynomolgus monkeys or rabbits were considered not to be related to treatment with TGN1412 but to the dose administration procedure.

Overall, the results of non-clinical studies in rodents and non-human primates have not revealed any potentially serious toxicities that would preclude the use of TGN1412 in healthy subjects. Based on a NOAEL of 50 mg/kg body weight, the clinical starting dose of 0.1 mg/kg body weight represents a safety margin of 500-fold, which is considered to be sufficient 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.

6. REPRODUCTIVE TOXICOLOGY

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.

In cross reactivity studies with human and cynomolgus monkey tissues [redacted] intracytoplasmic staining with TGN1412 that was considered to be specific was recorded in some keratinised epithelial cells in the cervix of cynomolgus monkeys and also in cytotrophoblast cells in the placenta of humans. This intracytoplasmic staining was not regarded as being of clinical importance as exposure of cytoplasmic antigens may be a result of tissue sectioning and no treatment related histology findings were reported for the genital system (testis, epididymis, ovary, uterus, and vagina) in the 28-day repeated dose toxicology study in cynomolgus monkeys.

FOIA 43(2)

7. GENEOTOXICITY

No genotoxicity studies have been performed since the standard battery of genotoxicity studies is not expected to deliver meaningful results for TGN1412. Due to the fact that TGN1412 acts by extracellular binding to the T cell surface molecule CD28, it is not anticipated that TGN1412 has a genotoxic effect.

Standard long-term carcinogenicity studies in rodents are not expected to deliver meaningful results for TGN1412 due to its species specificity for human and non-human primate CD28. In addition, long term studies with a humanized protein such as TGN1412 in animals may be difficult due to the immunogenicity of the drug. There is no evidence from available pharmacology and toxicology studies that TGN1412 has mutagenic or carcinogenic potential.

8. DISCUSSION

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.

The applicant has presented a reasonable preclinical data package and has made maximum use of data obtained from the 28 day pivotal monkey study. This study did not indicate any toxicological adverse effect.

The inclusion/exclusion criteria would appear adequate. There is no mention in these criteria about contraception, however, this is covered in the protocol as indicated under patient population above.

9. CONCLUSION

There are no preclinical objections to proposed CTA

REMARKS:

Name **Date: 06/01/2006**
Preclinical Assessor
[redacted]
*

Name **Date :** 24/01/2006
Preclinical Assessor
[redacted]
*

REMARKS

GNA Remarks
<GNA Remarks (remarks from Application Decision page with GNA outcome)>

* Name(s) withheld under Sections 36 and 38 of the FOI Act as, in MHRA's view, the public interest in disclosure is not outweighed by the public interest in maintaining that confidence.

CTA NUMBER	27431/0001/001-0001
EUDRACT No.	2005-003371-21
PRODUCT:	TGN 1412
APPLICANT:	TeGENERO AG

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

ANTICIPATED CLINICAL USE: Chronic inflammatory conditions and leukaemias

MEDICAL ASSESSMENT:

Background

TGN1412 is an agonistic anti-CD28 monoclonal antibody that specifically binds CD28 expressed on human T-cells, 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. 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. TGN1412 represents the first universal T-cell growth factor applicable for therapeutic purpose in the intact organism.

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). 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. 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.

TGN1412 has also 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 mechanisms 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.

A number of safety and efficacy studies with TGN1412 in non-human primates have been conducted using single- and multiple-dose regimens. TGN1412 was well tolerated at doses up to 50 mg/kg (NOAEL) for at least four consecutive weeks. No TGN1412-related signs of toxicity, hypersensitivity or generalized immuno-suppression were observed in these studies. In a local tolerance study, intravenous, perivenous, or intra-

arterial routes of TGN1412 administration were well tolerated and did not produce clinically significant irritation.

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 (Cmax) 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.

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. A maximum tolerated dose (MTD) may not be identified on this basis but rather on the basis of the effects of TGN1412 on the immune system. A transient enlargement of lymph nodes was occasionally observed in pre-clinical studies at high doses in the cynomolgus monkey, which were considered most likely to be related to the pharmacology of the study drug i.e. an excessive T-call reaction. Lymph node and spleen enlargement are to be closely monitored in this study.

This study is the first in man.

PROTOCOL: TGN1412-HV

OBJECTIVE(S) (Aim of Study) (SCOPE) **:** SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC, OTHERS

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.

DESIGN (Nature of Trial)**:** Single-centre, randomised, double-blind, placebo-controlled, single ascending-dose escalation trial.

Four single doses, administered intravenously per infusion to four groups (n=8, 6 on active treatment; 2 on placebo). Dose escalation to the next dose level will proceed following satisfactory review of safety data from at least 14 days following each dosing.

Subjects will be admitted to the Clinical Pharmacology Research Unit on Day -1 (CPRU) and stay there until Day 3. Vital signs will be measured at 0.5, 1, 2, 4, 8 and 12 hours after the start of the infusion. Further ambulatory visits are scheduled for Days 3 to 6,

Days 8, 10, 12, 15, 18, 22, 29 and 36. The final follow-up examination will be performed on Day 43.

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

POPULATION OF TRIAL SUBJECTS: Healthy male subjects aged 18 - 40 years

PROPOSED DOSAGE: TGN1412 intravenously per infusion 0.1, 0.5, 2 .0 and 5.0 mg/kg body weight or placebo

DURATION OF ACTIVE TREATMENT: Single dose

OVERALL DURATION OF TRIAL (EU): 4 Months

PROPOSED NUMBER OF PATIENTS INVOLVED (WW/EU/UK):
32
32
32

CONCLUSION:
Preclinical data indicate that TGN1412 is well tolerated. Safety assessments are appropriate and a Data Safety Monitoring Board will review the data before proceeding to the next dose. Safety reporting procedures are in place.

The risk:benefit ratio is favourable.

No objections.

REMARKS:

GNA Remarks:
<GNA Remarks (remarks from Application Decision page with GNA outcome)>

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MEDICAL ASSESSOR: [redacted]

ASSESSMENT DATE: 23/01/2006

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* Name(s) withheld under Sections 36 and 38 of the FOI Act as, in MHRA's view, the public interest in disclosure is not outweighed by the public interest in maintaining that confidence.