INVESTIGATIONS INTO ADVERSE INCIDENTS DURING CLINICAL TRIALS OF TGN1412

This is a summary report into the Medicines and Healthcare products Regulatory Agency (MHRA) investigations regarding the Serious Adverse Events experienced during the entry into man study of the monoclonal antibody TGN 1412. It summarises the inspections performed by the MHRA and other European authorities and the testing performed on samples following the incident.

BACKGROUND

Organisations involved in the trial

Role	Name	Location
Sponsor Product	TeGenero AG	Wurzburg, Germany
Manufacturer	Boehringher Ingelheim	Germany
Laboratory Studies	Animal Testing Laboratories*	
Contract Research Organisation for Phase I clinical trial	Parexel	Northwick Park Hospital, Harrow, UK

* MHRA is not revealing the name or location of the animal testing laboratories involved in the pre-clinical trials of TGN1412

Summary of Events

Parexel was contracted by the sponsor, TeGenero AG, to conduct an entry into man study of the monoclonal antibody TGN1412. The Medicines and Healthcare products Regulatory Agency (MHRA) authorises all clinical trials that take place in the UK. It conducts a rigorous scientific review of the data supplied by the applicant before authorising the trial.

Applicants will need to show that the product has been adequately tested and the tests must provide information on how the drug works, how it should be administered and how the body is likely to react to its administration.

The MHRA received an application for the authorisation of the clinical trial of TGN1412 on 23 December 2005. The clinical trial was authorised on 27 January 2006. All clinical trials also need to secure a favourable ethical opinion from a recognised ethics committee. Their purpose is to protect the rights, dignity and well-being of research participants. Brent Medical Ethics Committee gave a favourable opinion on 14 February 2006.

This was a first in man clinical trial undertaken at one centre which involved the administration of TGN1412 and placebos. Eight healthy male volunteers

were recruited by Parexel Clinical Pharmacology Research Unit (CPRU). As usual, neither the healthy volunteers nor the physician could identify which subjects received TGN1412 and which received the placebo. Four single doses: 0.1, 0.5, 2.0 and 5.0 mg/kg were planned to be administered to 32 subjects in 4 groups of 8. The first date of screening was 22nd February 2006. The first day of dosing was 13th March 2006.

On 13 March Serious Adverse Events (SAEs) were reported in 6 of the 8 subjects. According to Parexel CPRU, the subjects experienced a life – threatening incident of "Cytokine Release Syndrome". This occurs when the substance release by activated T cells produces a type of systemic inflammatory response.

Parexel confirmed that the all 6 subjects who received the active drug experienced SAEs. The two subjects who received placebo did not experience any adverse events.

The incidents were reported to the MHRA on the afternoon of 14 March. The MHRA

- Immediately suspended the Clinical Trials Authorisation
- confirmed that the drug in question was not in use in any other trial anywhere in the world
- alerted international drug regulatory authorities of the events, in case any similar drug of this class might be in use
- sent a team of inspectors to the unit in Northwick Park to secure documents, samples and other evidence (in liaison with the Metropolitan Police).

A programme of investigations was set in train to discover what had caused the reactions in the six men participating in the trial. Investigations were undertaken to ensure that procedures were in line with the internationally recognised standards for

- **Good Clinical Practice (GCP)**

  This covers all aspects of all stages of clinical trials to ensure they are dealt with safely and in accordance with legislative requirements. It also includes issues such as arrangements for the safety and wellbeing of the patient, patient consent and confidentiality of data.

- **Good Laboratory Practice (GLP)**

  This covers the conduct of non-clinical studies (ie those not involving humans) which assess the safety of new chemicals to man, animals and the environment. The range of test facilities inspected and monitored include those involved in the testing of human and veterinary pharmaceuticals, agrochemicals, cosmetics, food and feed additives and industrial chemicals.

- **Good Manufacturing Practice (GMP)**

This covers the activities of pharmaceutical manufacturers to ensure that medicines supplied in the UK meet consistent high standards of quality, and of safety and efficacy. Overseas sites named as manufacturing sites for products with UK marketing authorisations are also inspected.

Possibilities under consideration during the investigations included:

- A dosing error, with all participants being given an overdose
- An error in the formulation or dilution of the drug (either in the clinical trials unit, or in its original manufacture in Germany), which could also potentially lead to an overdose
- Contamination of the drug with some other toxic substance
- A previously unknown biological effect on humans that did not arise in any of the animal testing phases.

Inspections assure the integrity of the data being submitted. Inspections were performed at the following facilities and included examination of facilities, records and interviews with staff.

Facility	Inspection Type	Date of Inspection	Inspector(s)
TeGenero, Germany	Good Clinical Practice (GCP)	17th of March 2006	Paul Ehrlich Institute (PEI – the German Regulatory Authority)
Parexel, Harrow, UK	GCP	16th, 17th and 27th March 2006	MHRA.
Parexel	Good Manufacturing Practice (GMP)	14th and 16th March 2006	MHRA
Animal testing Laboratories	Good Laboratory Practice (GLP)	20th-21st March 2006	MHRA
Boehringher, Ingelheim, Germany	GMP	22nd – 24th of March 2006	PEI observed by MHRA inspector

INSPECTION FINDINGS

GCP Inspection of TeGenero

The inspection by the German Regulatory authorities focused upon the preclinical work performed by TeGenero prior to the first in man study. This includes tests on animals undertaken to support the proposal that the drug can be tested in humans. All company records and processes were examined to

establish whether all relevant studies had been completed correctly and proper data included in the Clinical Trials Application as required by legislation – in particular whether there was evidence of undisclosed studies. No deficiencies were found.

GCP Inspection of Parexel

All company records and processes were examined and staff interviewed to establish whether all relevant clinical studies had been completed correctly by Parexel and whether any aspect of the way the trial was conducted might have led to the reactions- in particular, arrangements for dose measurement and administration of the drug. There was no finding of any deficiencies which would have directly contributed to the Serious Adverse Events experienced by the trial subjects who received TGN1412.

GMP Inspection of Parexel

The scope of the inspection were the facilities, equipment, quality systems, documentation and records associated with the storage, preparation and release of TGN 1412 and placebo at the Parexel unit. This would include whether the preparation of the drug in the unit might have led to contamination or overdose. No deficiencies were discovered during the inspection.

GLP Inspection of Animal Testing Laboratories

The purpose of the inspection was to determine that a pivotal toxicology study performed to support the progression of TGN1412 into man was conducted in accordance with the principles of GLP. The particular study audited was a

"4 week intravenous toxicity study in cynomolgus monkeys with a 6 week observation period".

Additionally two validation studies and a dose ranging study were also reviewed. The inspector concluded that the study had been performed in accordance with the principles of GLP and that the results presented in the final report appeared to accurately reflect the raw data. No critical or major deficiencies were identified which would have directly contributed to the Serious Adverse Events experienced by the trial subjects who received TGN1412.

GMP Inspection of Boehringer Ingelheim

A product and process specific inspection of TGN1412 and the placebo was conducted by the German Regulatory Authorities and this was observed by an inspector from the MHRA. The scope of the inspection was the manufacture, testing, storage and distribution of TGN1412 and the placebo. No deficiencies were identified which would have directly contributed to the Serious Adverse Events experienced by the trial subjects who received TGN1412.

Product Testing

Following the incident a series of tests are being performed by independent laboratories to determine if the products met the batch release specification. Additional tests are being performed to aid the investigation into the incident. The testing is not yet completed but the results to date are consistent with the agreed specification for TGN1412. Tests are also underway to assess bacterial contamination. Results so far do not suggest this.

CONCLUSIONS

Subject to the completion of the outstanding tests, MHRA takes the view that the adverse incidents did not involve errors in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants. The MHRA therefore concludes that an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions in the trial participants. Monoclonal antibodies are a relatively new type of biological drug although there are a number of them already licensed and in use. However, TGN1412 is a new class of monoclonal antibody which has a stimulatory mode of action affecting certain types of cell in the immune system. In this case the resulting activity seen in humans was not predicted from apparently adequate pre-clinical testing. This is a complex scientific issue which raises important scientific and medical questions about the potential risks associated with this type of drug and how to make the transition from pre-clinical testing to trials in humans.

Establishment of an Expert Group

The issue will attract international interest and could potentially affect clinical trials regulation worldwide. The Secretary of State for Health has therefore agreed to establish a group of leading international experts in the field to consider this issue with membership appointed from distinguished experts in the relevant fields of enquiry, including immunology, toxicology and clinical trials. The Group will need to review the evidence from the TGN1412 case and consider what necessary changes to clinical trials may be required. It will be convened under the auspices of the Commission on Human Medicines which has among its statutory duties to advise the Secretary of State on matters affecting the safety of medicines.

The Secretary of State has appointed Professor Gordon Duff to act as Chair of the group. Professor Duff is Professor of Molecular Medicine at Sheffield University with an international reputation in his field.

The proposed terms of reference for the Expert Group are:

> "1. To consider what may be necessary in the transition from pre-clinical to first-in man Phase 1 studies, and in the design of these trials, with specific reference to:
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> - Biological molecules with novel mechanisms of action;
> - New agents with a highly species-specific action;

- New drugs directed towards immune system targets.

2. To provide advice in the form of a report to the Secretary of State for Health for the future authorisation of such trials with an interim report to be provided within three months”

Interim Measures

Until the Expert Group has completed its work, the MHRA will take a precautionary approach for all further clinical trial applications involving first-in-man trials of any monoclonal antibody (regardless of intended target) or other novel molecules targeting the immune system, acting via a novel mechanism. Such trials will be not be authorised without having had additional expert opinion on whether the effects seen in the TGN1412 case may be repeated in relation to those substances.

Further Information

When all investigations are complete, the MHRA will release a further statement setting out findings and conclusions In the meantime, the work of the Expert Group will be taken forward.