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## POSITION PAPER

*Helsingborg, March 29, 2006*

# Clinical Trials with healthy volunteers

### Background

A phase I clinical trial, with a monoclonal antibody in healthy volunteers, was initiated on the 13 March 2006 at Northwick Park Hospital situated in North London. Eight young men participated in the trial, six of whom received the active ingredient and two received placebo. Almost immediately after being dosed with the drug the six men started to complain about intense pain and breathing difficulties. Within a short space of time all six were unconscious and were transferred to the hospital's intensive care unit for treatment. Four of them have now regained consciousness whilst the remaining two are still unconscious and their condition is deemed to be critical.

The trial was conducted by PAREXEL, a contract research organisation on behalf of a German biotech company. The drug – TGN 1412 – is a monoclonal antibody which is planned to be used in the treatment of chronic lymphatic leukaemia, rheumatoid arthritis and multiple sclerosis.

Preclinical tests in animals have not shown anything that could explain what has happened to the healthy volunteers in this trial. The trial was approved by an Ethics Committee and the Regulatory Authority, The Medicines and Healthcare products Regulatory Agency (MHRA).

The event has been covered extensively across the media throughout the UK but even in the rest of Europe and the USA. It is difficult to explain what has happened but there are researchers/doctors who believe that previous trials with monoclonal antibodies have indicated that this type of tragedy could happen. The compound could have triggered the normal immune system to run amok - cytokine storm. A cytokine storm can cause the body's own immune system to turn against a healthy individual's organs and bodily functions.

Critics have pointed out that the drug should have been tested in "patients" first, and that the company should have administered the drug more carefully in order to monitor its effects in man. The company has also been criticised because they paid the young men approximately 3000 Euros for their participation.

The health authorities in England have now stopped all studies with TGN1412 until further notice and an inquiry has been started to find out what happened, why and if the tragic event could have been avoided. The inquiry will take up to several months before it is completed.

### Consequences

There are several possible consequences of the event at Northwick Park Hospital:

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1. Regulatory Authorities worldwide will be much more careful before approving trials with this kind of drug in the future.
2. There will probably be new guidelines for conducting trials with monoclonal antibodies in the future.
3. It will be more difficult to motivate healthy volunteers to participate in trials with new drugs especially if they are first in man studies.
4. Regulatory Authorities (but even companies) will be more positive to microdosing studies, as one uses drugs in very small doses
5. The general public's attitude to clinical research will be more negative.
6. The English health authorities – MHRA – have already been criticised for their rapid evaluation of phase I clinical trials (approximately 15 days for single centre trials). In the future they might take as much time as other European Regulatory Authorities. The MHRA has also been criticised for not using specialists in this field but it is difficult to assess this criticism.

### TFS Trial Form Support's position

TFS Trial Form Support manages more than 15 phase I trials for different clients every year. The majority of these trials are run at the TFS phase I unit at the Karolinska University Hospital in Stockholm, Sweden. This service is an important part of the services that TFS Trial Form Support offers our customers and we see no reason to stop this activity. TFS Trial Form Support is very careful as to how we manage these projects:

- The phase I unit Managers at TFS Trial Form Support and Karolinska University Hospital hold detailed discussions about studies to be performed at the unit and always perform a risk benefit analysis. If there is any doubt about any additional risk then the client is recommended to have an advisory meeting with the relevant Competent Authority.
- TFS Trial Form Support always recommends an alternative design to trials in order to minimise the risk for participants. If it is deemed that the trial cannot be performed without undue risk to the participants then the client is informed that TFS Trial Form Support will not conduct the trial.
- All trials are approved by the Ethics Committee and the Regulatory Authority before they can begin.
- All trials are performed in accordance with GCP (Good Clinical Practice), which means amongst other things that all healthy volunteers will be personally informed as to the possible risks of participating in the study. Participants also approve their willingness to participate in the trial in writing.
- All trials are audited by the Quality Assurance department at TFS Trial Form Support irrespective of whether this has been requested by the client or not.
- The phase I unit has access to the hospitals intensive care unit with specialist staff who are trained to look after patients in an emergency.
- Healthy volunteers are paid a reasonable sum of money as compensation for their participation in phase I trials. There must never be any suspicion that healthy volunteers have been "bought" to participate in the trial. If we have any doubt as to what is a reasonable sum as compensation then TFS Trial Form Support contacts the relevant Ethic Committee for advice.
- All instructions from the Regulatory Authorities are implemented immediately.

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With all this taken into consideration we at TFS Trial Form Support believe that we have done everything we can to minimise the risk for participants coming to harm when participating in clinical trials conducted by us.

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