

## *newsletter*

# Insurance for clinical trials

**In early 2006, a new biological medicinal product had unexpected, life-threatening side effects on six male volunteers during clinical trials.**

### **Introduction**

Clinical trials are essential to medical progress and thus make a valuable contribution to the prosperity of society. They also form the basis for the authorisation process for new medicines, whose efficacy and safety when given to humans can be demonstrated only in practical trials. They also grant many patients an opportunity to profit from the latest therapies. Strict rules governing clinical trials ensure a very high standard of safety for test subjects. As a result, the claims history of, for example, Phase I trials (first studies to determine an agent's compatibility and identify its effects on healthy humans) can be assessed as very satisfactory on the whole: it is extremely rare for test subjects to suffer serious health impairment. Nevertheless, some risk remains, especially in Phase I trials.

### **Recent events**

During a recent Phase I trial in the UK, all six test subjects suffered unexpected life-threatening side effects. The medicine being tested (TGN1412) caused severe reactions culminating in multi-organ failure (MOF) that required intensive care. All six participants survived, but at least one volunteer's health has been permanently impaired.

The medicine being studied in the trial, a monoclonal antibody, was being tested on humans for the first time. In principle, the agent was supposed to trigger complex cascades to stimulate certain immune cells, known as T cells, and thus to open up new approaches to treating chronic lymphatic leukaemias and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (the grounds stated in the application for authorisation). Unlike most monoclonal antibodies already authorised, the aim of which is to prevent/suppress an immune response (antagonists), TGN1412 was intended to activate the immune system (an agonist). As it also affects a central control mechanism of the immune system, the monoclonal antibody TGN 1412 is also called a "super-agonist". By contrast with the effects observed in experiments on animals, where only certain regulatory T cells were activated, when the agent was administered to humans, even though in a much lower dose, it obviously also stimulated further non-specific lines of T cells. These in turn produced large quantities of chemical signalling compounds ("cytokines") which in cascade responses activated further elements of the immune system (excessive immune response). It was this response, known as the "cytokine release syndrome", which led to the multi-organ failure in the test subjects. Investigations by the UK Medicines and Healthcare products Regulatory Agency (MHRA) came to the conclusion that the side effects were due to the inherent properties of the medicines being tested and not to any technical quality defect or any failure to comply with the protocol drawn up for the trial.

**Clinical trials, phases, authorisation of medical products**

Directive 2001/83/EC on the creation of a Community code for medicines for human use is the cornerstone of the authorisation of medical products in the EU and in Liechtenstein, Iceland and Norway. There are various possible authorisation procedures: a central procedure via the European Medicines Agency (EMA), a decentralised authorisation procedure, and a mutual recognition procedure. In Germany, the Pharmaceuticals Act (AMG) provides the statutory basis for performing clinical trials.

Clinical trials can get under way only when the competent authorities (in Germany the Federal Institute for Drugs and Medical Devices, BfArM, or the Paul-Ehrlich-Institut, PEI) have given their approval and if an Ethics Committee has voted in favour. Before a medicine is authorised, its harmlessness, efficacy and safety have to be proven in a series of trial phases, often on several thousand test subjects and patients.

- Phase I: performed on a small group of healthy test subjects to determine the agent's compatibility, safety for use as a medicine, pharmacokinetics),
- Phase II: performed on a few actual patients to establish a safe dose, observe any side effects and obtain initial information on efficacy,
- Phase III: performed on several thousand patients to obtain objective proof of efficacy and to draw up a statistically significant profile of side effects.

**Insurance for clinical trials**

In Germany, § 40 para 1 No 8 AMG makes liability cover for harm caused to test subjects compulsory before a clinical trial can be conducted (one of the preconditions for an exemption from the formal ban on clinical trials; limit of indemnity at least EUR 500 000). In Switzerland, insurance is not compulsory, but there is a statutory duty to provide security, which is ultimately fulfilled in the form of insurance taken out to cover the test subjects.

Ref: apropos Clinical Trials; AssTech, 2002.

**Exposure**

Determining the liability insurer's clinical trials exposure calls for precise analysis of the specific risk and a special expertise. An essential criterion for the technical risk assessment is the quality of the trials themselves: globally recognised quality standards (eg GCP, GMP, GLP) govern the procedures used in clinical trials. Important parameters include meticulous planning and performance in accordance with a detailed protocol based on appropriate criteria for inclusion and exclusion of test persons (methodology), a positive opinion by an ethics committee, details of the sponsors and the persons conducting the trials, clearly formulated objectives, and especially the informed consent form – legally vetted, if possible.

Further criteria concern the type of substance to be tested and how it works, the dose and duration, and the type of treatment (eg how the substance is administered, intervals between doses). Particular attention should be paid to substances with the following features:

- new chemical entities, eg having a new mechanism of action,
- where there is no suitable animal model for the point of action in the human body,
- the substances penetrate the immune system (eg monoclonal antibodies),
- the substances intervene in the metabolism of the brain,
- the substances have a narrow therapeutic bandwidth.

- agents to be administered to babies or toddlers,
- agents for which authorisation is also sought for use by pregnant women.

Generally speaking, trials involving agents that are being tested on humans for the first time (Phase I following experiments on animals) entail the highest uncertainties, whereas the risks of bioequivalence studies on known substances (generics) whose side effects have already been described are easier to assess. The same applies to trials involving medical products whose risk stems eg from the permanent implant.

General information of importance to a risk analysis includes: number, age and sex of the test subjects, duration of the trial, type of trial and countries in which it is conducted, trial phase, other medicines allowed to be administered at the same time, invasive actions.

### **Information for the underwriter**

Clinical trials are essential to medical progress. Strict laws and regulations have achieved a high level of safety for the participating test subjects and patients. Nevertheless, some risk always remains. To provide at least financial compensation for any harm suffered, liability insurance for the test subjects has to be in place before any clinical trial is allowed to start in Germany.

Underwriting the risk inherent in these individual covers calls for a special expertise (risk assessment). This is not limited only to the agent or medical product to be tested, but also takes into account a number of further factors such as organisational aspects, the information given to the test subjects to obtain their informed consent, the selection of patients and volunteers, criteria for inclusion and exclusion of candidates.

Special attention should be given to Phase I trials and to trials involving highly exposed groups of people such as children or persons with suppressed immune systems. New EU legislation prescribes that, for all new medicines in the authorisation pipeline as of 2007, special studies must be carried out on children. This can mean more clinical trials being extended to include children, which would have a positive effect on the safety of the agents but would have to be taken into account in the risk assessment for the insurance cover.

Clinical trials involving biological medicines are a particularly touchy issue, because of the complex ways in which these substances work. Even if serious events such as the case mentioned in the introduction are an extremely rare exception, these trials should be watched particularly carefully. It remains to be seen which consequences the (national, international) authorities will draw from this incident and what action will be taken to improve the safety of the test subjects. Among the enhanced precautions currently being discussed are new protocols specifically adapted to the particular risk or special risk management approaches (eg time intervals between administering the test substance to successive human subjects).

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