Phase I Trials

Introduction

Phase I trials are usually the first studies of a medicine conducted in humans – known as 'first-in-human' (also known as first-in-man) trials. They are typically human pharmacology studies. Before Phase I trials begin, the medicine will have been thoroughly and extensively tested in laboratory and animal studies; known as non-clinical testing.

Key questions for Phase I trials

Phase I studies seek to answer the following questions about a new medicine:

- Is the medicine safe in humans? At what levels? (Tolerance)
- What does the body do to the medicine? (Pharmacokinetics (PK))
- What does the medicine do to the body? (Pharmacodynamics (PD))
- What interactions are there? (Drug-Drug interactions, interactions with food and drink, etc.)
- Is the medicine active?

[glossary_exclude]Characteristics of Phase I trials

Location

Phase I clinical trials are often conducted at dedicated in-patient clinics where the participants can be observed by experienced, full-time staff. First-in-human trials are preferably conducted at a single site, with all possible

safety provisions in place in the case of unexpected serious adverse reactions. These safety provisions include immediate access to equipment and staff for an acute emergency and ready availability of Intensive Care Unit facilities. The provisions are laid down in the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (London, 20 July 2017 ; Doc. Ref. EMEA/CHMP/SWP/28367/07 Rev. 1)'.[/glossary_exclude]

Participants

Phase I trials are usually conducted in healthy volunteers, as the objectives of Phase I trials are generally non-therapeutic. A minority of Phase I trials are conducted in patients because some investigational medicinal products (such as anti-cancer treatments) are too toxic to be given to healthy participants.

Compensation

Participants in Phase I trials may be compensated in accordance with local laws. Compensation in terms of payment to participants must never be related to risk, and the amount of compensation must be reviewed by an ethics committee and stated in the informed consent document signed by participants before the study.

Risk

In spite of extensive and thorough non-clinical testing, the side effects that the investigational medicinal product may have in humans cannot be completely known ahead of first-in-human trials. As a result of this uncertainty, Phase I trials may involve significant risks. The potential risk is identified from animal models, previous exposure of humans to medicines with related modes of action, the nature of the target, and other considerations.

[glossary_exclude]Risk mitigation in Phase I trials

There can be significant risks associated with participation in Phase I trials. The European Medicines Agency has issued guidelines on the identification and mitigation of risks for participants in first-in-human trials. (EMEA/CHMP/SWP/28367/07 Rev. 1)[/glossary_exclude]

Key factors that are considered in order to mitigate risks are:

- Study population
- Trial sites
- First dose
- Route and rate of administration
- Number of participants per dose (cohort)
- Sequence and interval between dosing of participants within the same cohort
- Dose escalation increments
- Transition to the next dose cohort
- Stopping rules
- Maximum Tolerated Dose (MTD)

Quality aspects

The requirements are the same for all investigational medicinal products regarding physical and chemical characterisation, biological activity and, additionally, biological characterisation of biological products. Quality attributes should not, in themselves, be a source of risk for first-in-human trials. However, these quality attributes are to be considered in a risk assessment preceding a first-in-human trial.

Specific points to be considered are:

- Determination of safe starting dose (strength and

potency)
- Qualification of the material used
- Reliability of very small doses