Fact Sheet: Making a medicine – Proof of Mechanism studies

Phase I Clinical Studies

The decision to continue to the first clinical study is a major one. As a candidate compound continues through the development process, the number, cost, and complexity of the activities surrounding the study all increase.

Before starting a clinical study, a Clinical Trial Application (CTA) must be submitted. The CTA must include the following important documents:

- An Investigational Medicinal Product Dossier (IMPD), including ADME and studies to observe effect (on the target), the toxicology safety, and information on how the medicine is manufactured
- The Study Protocol describing the details of performing the study and evaluating the results
- The Investigator's Brochure (IB), providing a summary of the information that allows the doctors who run the study (the investigators) to understand how the study compound works in the body (the pharmacology). This allows the investigators to explain the study to the volunteer or patient and to obtain informed consent (see below).

Safety is the top priority. Therefore, a study in humans cannot start until the Internal Company Review Committee, the External Ethics Committee and the External Regulatory Authority have given their approval.

Volunteer Study (also called Exploratory study, Proof of Mechanism study, or Phase I study)

These studies allow the doctors and scientists to see if the candidate compound is safe in humans. They also look at whether the medicine behaves in humans in the same way it behaved in animals. These studies provide information on the way that the candidate compound works – called the 'mechanism of action'.

Approximately 20 – 100 volunteers are included in Phase 1 studies. These studies are usually carried out in special Phase 1 units where the volunteers are recruited and the studies are run. The doctors who carry out these studies are called Investigators and they are qualified to conduct clinical trials in order to determine the outcome of the study.
The first clinical study is usually carried out in healthy, male volunteers. The details of the clinical study have to be described in the Study Protocol. All the information is collected in a document called the Case Record Form (CRF).

Here, too, there is a large number of guidelines and regulations – known as Good Clinical Practice (GCP) – to protect the safety of the subjects in the study.

The Study Protocol also has a section on 'statistics', which are the statistical tests used to analyse the results. These directions must be decided before the study starts.

Two very important rules are:

- informed consent (ensuring that the participants understand what is going to done and agrees to be part of the study), **and**
- Ethics Committee review and opinion.

The Ethics Committee is an independent group, usually consisting of doctors, scientists, nurses, and non-experts ('lay members'). They review the study protocol (especially the informed consent form) and ensure that it complies with the ethical regulations of the committee before the study is carried out.

As safety is a priority, the first clinical study starts with a very low dose of the medicine.

- A single dose of the medicine is used for each volunteer.
- Once it has been shown that there are no safety concerns with this first dose, the study can continue with a slightly higher dose.
- The dose will then be further increased ('ascending dose') until the maximum dose allowed for the study has been reached.

This is described in the Study Protocol.

The study results can then be analysed and all the safety measurements can be assessed. This includes the:

- pharmacokinetics – what the body does to the medicine. The blood levels of the medicine can be measured – to determine the Absorption, Distribution, Metabolism and Excretion (ADME)
- pharmacodynamics – what the medicine does to the body (the 'effect'). For example, the study might measure the effect of a medicine on certain blood cells.

This type of study is known as a Single Ascending Dose (SAD) study. This is usually followed by a Multiple Ascending Dose (MAD) study which, as the name suggests, involves multiple doses per volunteer.

Other Phase I studies are also needed in addition to the SAD and MAD studies – for example, studies investigating the effect of food or other medicines on the function of the candidate compound.