Setting the ‘first-in-human’ dose

Introduction

The progression from non-clinical testing to human clinical studies is an important step in the development of a medicine. Before taking this step, previous data must be considered and careful decisions made – not least about the first dose to administer to patients.

For many innovative medicinal products, an estimation of a safe starting dose is sufficient. However, such an estimation may not be sufficiently predictive of serious adverse reactions for some candidate compounds. Risk factors and mitigation measures must be assessed and discussed before any first-in-human clinical trials begin; these risk factors should be considered on a medicine-by-medicine basis.

Risk factors

Risk factors might relate to the mode of action of the medicine. It is therefore relevant to assess:

- previous human exposure with related substances,
- the structure of the medicine, **and**
- evidence from the animal models of potential toxicity.

Other considerations of risks include:

- the nature of the target,
- intensity effects, **and**
- the dose-response relationship.

There are some risk factors that may require special attention. For instance:

- metabolic pathways,
- genetic differences in relevant animal species and humans.

Considerations in establishing first-in-human dose

The clinical starting dose depends on various factors, including pharmacodynamics, particular aspects of the candidate compound, and the proposed design of the clinical trials. Some other important factors to consider when the first-in-human dose is established include:

- All relevant non-clinical data, including
  - Pharmacological dose-response studies,
  - Pharmacological/toxicological profile, **and**
  - Pharmacokinetics studies.
- The No Observed Adverse Effect Level (NOAEL)
  - The level of exposure of an organism at which there is no significant increase in the frequency or severity of any adverse effects. This is the most important information for consideration.

Approaches to dose-setting

There are two classical approaches to estimating the first-in-human dose in Phase I clinical trials:

1. Based on the established NOAEL in toxicity studies and taking individual growth into consideration, the first human dose can be determined with the application of the relevant safety factor.
2. In the case of many biotechnology-derived medicines, and when risk factors have been identified, the first-in-human dose is established using the Minimal Anticipated Biological Effect Level (MABEL) standard and the application of the relevant safety factor. To estimate

the MABEL, all relevant non-clinical data available is taken into consideration.

The safety factor is set by considering the criteria of risks, such as the novelty of the active ingredient, its biological potency, its mode of action, the degree of species specificity, and the dose-response.

The Committee for Medicinal Products for Human Use (CHMP) issued a guideline in 2007, comprising strategies to identify and mitigate risks for first-in-human clinical trials with high-risk investigational medicinal products.[1]

Dose-setting in exploratory clinical trials

Early access to human data can improve insight into human physiology/pharmacology, knowledge of a candidate compound's characteristics and therapeutic target relevance to the disease. The concept of 'exploratory clinical trials' (Phase 0) has been developed to satisfy this need. Exploratory trials comprise different approaches than traditional clinical trials: such trials are to be conducted before or early in Phase I, involve limited human exposure, have no therapeutic intent, and are not intended to examine clinical tolerability.

As such, exploratory clinical trials may be initiated with different, non-clinical support; in such cases, the factors considered during the estimation of the clinical starting (and maximal) dose can differ.

[glossary_exclude]Further resources

- European Medicines Agency (2023). *Scientific advice and protocol assistance*. Retrieved 18 February, 2024, from https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-

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- National Institutes of Health (2015). *Principles and guidelines for reporting preclinical research*. Bethesda, MD: NIH. Retrieved 28 July, 2015, from http://www.nih.gov/about/reporting-preclinical-research.htm
- Committee for Medicinal Products for Human Use (2017). *EMEA/CHMP/SWP/28367/07 Rev. 1 Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products*. London: European Medicines Agency. Retrieved 18 February, 2024, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf[/glossary_exclude]

[glossary_exclude]References

1. Committee for Medicinal Products for Human Use (2017). *EMEA/CHMP/SWP/28367/07 Rev. 1 Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products*. London: European Medicines Agency. Retrieved 18 February, 2024, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf[/glossary_exclude]

[glossary_exclude]Attachments

- Presentation: Non-Clinical Development

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  Presentation on aspects of non-clinical development, including its aims, background activities, and the different types of non-clinical study.

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