Non-clinical requirements before first-in-human studies

Introduction

Before a candidate compound may be administered to humans as part of Phase I (first-in-human) clinical trials, it must undergo rigorous safety and efficacy testing in non-clinical studies.

The International Conference on Harmonisation (ICH) has laid out the requirements that must be satisfied by the non-clinical programme before a candidate compound may be administered to humans.[1] ICH Module 3 (Non-clinical testing) requires the following studies be conducted:

- pharmacology studies,
- general toxicity studies,
- toxicokinetic and non-clinical pharmacokinetic studies, **and**
- repeated-dose toxicity studies.

Some further non-clinical studies are conducted on a case-by-case basis according to specific conditions, including for instance:

- assessments of carcinogenic potential
- phototoxicity, immunotoxicity, juvenile animal toxicity, etc.
- biotechnology-derived products (guideline issued under ICH topic S6[2])
- life-threatening or serious diseases – such as resistant HIV infection or congenital enzyme deficiency diseases that don’t have a current effective therapy
- medicines using innovative therapeutic modalities (for

example, siRNA or vaccine adjuvants) where non-clinical studies can be shortened, postponed, left out, or added in the non-clinical programme.

The goals of the non-clinical safety assessment programme include, more specifically, the characterisation of toxic effects, the identification of target organs, clarification of dose dependence, the relationship of toxicities to exposure, and potential reversibility.

The table below shows the standard non-clinical programme that must be completed before the clinical programme may begin.

Standard non-clinical study programme before 'first-in-human' clinical trials. In this phase, single dose, data on lethality, and reproductive studies are not generally required. Table adapted from ICH (2009) M3(R2).

Type of study	**Aim of study**
Safety pharmacology core studies	Assessing effects on cardiovascular, respiratory, and central nervous systems (CNS).
Primary pharmacodynamics studies	*In vivo* and/or *in vitro* studies, assessing mode of action/effects of candidate compound on the target.
Pharmacokinetics and toxicokinetics studies	Data gathered during *in vitro* studies on metabolic and blood protein binding data for animals and humans. Systemic exposure data from toxicology studies.
Acute toxicity studies	Single-dose toxicity studies in two mammalian species – but can be completed during studies that define a maximum tolerated dose in the species used for toxicity testing.

Type of study	Aim of study
Repeated-dose toxicity studies	Vary in length according to duration, therapeutic indication and scope of the proposed clinical programme. Minimum duration for two weeks in two species (one of which is not a rodent).
Other studies of concern	For instance, investigation into phototoxicity (causing a reaction of the skin when exposed to light)

The repeated-dose toxicity studies in animals are designed to include a similar or longer exposure time than the intended clinical trial duration in humans (see table below). As shown, repeated-dose toxicity studies in two species (one non-rodent) for a minimum duration of two weeks would generally support any clinical trial of up to two weeks in duration. Clinical trials of longer duration should be supported by repeated-dose toxicity studies of at least equivalent duration. Six-month rodent and nine-month non-rodent studies generally support treatment for longer than six months in clinical trials.

Recommended duration of repeated-dose toxicity studies to support the conduct of clinical trials. Table adapted from ICH (2009) M3(R2).

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
Longer than 6 months	6 months[b,c]	9 months[b,c,d]

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials
[a] In the United States, as an alternative to two-week studies, extended single-dose toxicity studies can support single-dose human trials.[b] In some circumstances, clinical trials of longer duration than three months can be initiated, provided that the data are available from a 3-month rodent and a 3-month non-rodent study. On a case-by-case basis, this extension can be supported by chronic, in-life and necropsy data[c] There can be cases where a paediatric population is the primary population, and existing animal studies have identified developmental concerns. In these cases, long-term toxicity testing in juvenile animals can be appropriate.[d] In the EU, studies of six months duration in non-rodents are considered acceptable. However, where studies with a longer duration have been conducted, it is not appropriate to conduct an additional study of six months.	

The recommendations for the duration of repeated-dose toxicity studies needed to support a marketing authorisation application (MAA) are shown in the table below.

Recommended duration of repeated-dose toxicity studies to support marketing. Table adapted from ICH (2009) M3(R2).

Duration of Indicated Treatment	Rodent	Non-Rodent
Up to 2 weeks	1 month	1 month
More than 2 weeks to 1 month	3 months	3 months
More than 1 month to 3 months	6 months	6 months
More than 3 months	6 months[a]	9 months[a,b]

Duration of Indicated Treatment	Rodent	Non-Rodent
[a] There can be cases where a paediatric population is the primary population, and existing animal studies have identified developmental concerns. In these cases, long-term toxicity testing in juvenile animals can be appropriate.[b] In the EU, studies of six months duration in non-rodents are considered acceptable. However, where studies with a longer duration have been conducted, it is not appropriate to conduct an additional study of six months.		

References

1. International Conference on Harmonisation (2009). *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals M3(R2)*. *Step 4* Geneva: ICH. Retrieved 11 July, 2021, from https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf
2. International Conference on Harmonisation (2011). *Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)*. *Step 4* version. Geneva: ICH. Retrieved 11 July, 2021, from https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

Attachments

- Presentation: Non-Clinical Development

  Size: 478,517 bytes, Format: .pptx

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

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