Summary of Nonclinical Safety Studies Needed Prior to Each Phase of Clinical Trials

STUDY TYPE	REQUIREMENT
Prior to Phase 1	
Toxicity Studies	• Single-dose acute toxicity studies in two mammalian species required prior to Phase 1 • Repeated dose studies in two mammalian species (one rodent, one non-rodent) are required Prior to Phase 1 • The recommended duration of the repeated dose toxicity studies is usually related to the duration, the therapeutic indication, and scale of the proposed clinical trial • In principle, the duration of the animal toxicity studies conducted in two mammalian species (one non-rodent) should be equal to or exceed the duration of human clinical trials (see Table 1 below)
Reproduction Toxicity Studies	Reproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed. • Men may be included in Phase 1 trials prior to the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated dose toxicity studies • Women not of childbearing potential (i.e., permanently sterilized, postmenopausal) may be included in clinical trials without reproduction toxicity studies provided the relevant repeated dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted **US:** for women of child-bearing potential, reproduction toxicity studies are not required before Phase 1 with appropriate precautions (i.e., use of contraception, pregnancy testing) **EU**: reproduction toxicity are required prior to Phase 1 anytime women of child-bearing potential are to be enrolled **Japan:** assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial.
Safety Pharmacology Studies	• Assessment of effects on vital functions (central nervous, cardiovascular and respiratory system) needed prior to Phase 1 • These evaluations may be conducted as additions to toxicity studies or as separate studies
Toxicokinetic and Pharmacokinetic Studies	• Exposure data in animals should be evaluated prior to human clinical trials • Further information on ADME in animals should be made available to compare human and animal metabolic pathways. • Appropriate information should usually be available by the time the Phase 1 Human Pharmacology studies have been completed
Genotoxicity Studies	The following In vitro tests are generally needed prior to first human exposure: • Test for gene mutation in bacteria • In vitro test with cytogenetic evaluation of chromosomal damage within mammalian cells or an in vitro mouse lymphoma tk assay
Local tolerance Studies	Local tolerance should be studied in animals using routes relevant to the proposed clinical administration prior to human exposure. The assessment of local tolerance may be a part of other toxicology studies

The information presented in this table was taken directly from the FDA ICH M3, S1A, and S2B Guidance Documents

Summary of Nonclinical Safety Studies Needed Prior to Each Phase of Clinical Trials

STUDY TYPE	REQUIREMENT
Prior to Phase 1 (continued)	
Repeated Dose Toxicity Studies	The recommended duration of the repeated dose toxicity studies is usually related to the duration, therapeutic indication, and scale of the proposed clinical trial (refer to Table 1 below).

Table 1

Duration of Repeated Dose Toxicity Studies to Support Phase 1 and 2 Trials in the EU and Phase 1, 2 and 3 Trials in the US and Japan*

Duration of Clinical Trials	Rodents	Non-rodents
Single Dose	2 Weeks**	2 Weeks
Up to 2 Weeks	2 Weeks**	2 Weeks
Up to 1 Month	1 Month	1 Month
Up to 3 Months	3 Months	3 Months
Up to 6 Months	6 Months	6 Months***
> 6 Months	>6 Months	Chronic***

*In Japan, if there are no Phase II clinical trials of equivalent duration to the planned Phase 3 trials, conduct of longer duration toxicity studies should be considered (refer to Table 2)

**In the EU and the US, 2-week studies are the minimum duration. In Japan, 2-week nonrodent and 4-week rodent studies are needed (also refer to Table 2). In the US as an alternative to 2-week studies, single dose toxicity studies with extended examinations can support single dose human trials.

***Data from 6 months of administration in nonrodent should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9-month nonrodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.

Prior to Phase 2	
Reproduction Toxicity Studies	Reproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed. • Men may be included in Phase 2 trials prior to the conduct of the male fertility study since an evaluation of the male reproduction organs is performed in the repeated dose toxicity studies • Women not of childbearing potential (i.e., permanently sterilized, postmenopausal) may be included in clinical trials without reproduction toxicity studies provided the relevant repeated dose toxicity studies (which include an evaluation of the female reproduction organs) have been conducted **US:** for women of child-bearing potential, reproduction toxicity studies are not required before Phase 2 with appropriate precautions (use of contraception) **EU**: reproduction toxicity are required prior to Phase 1 anytime women of child-bearing potential are to be enrolled **Japan:** assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial.
Genotoxicity Studies	• An in vivo test for chromosomal damage using rodent hematopoietic cells

The information presented in this table was taken directly from the FDA ICH M3, S1A, and S2B Guidance Documents

Summary of Nonclinical Safety Studies Needed Prior to Each Phase of Clinical Trials

STUDY TYPE	REQUIREMENT
Prior to Phase 3	
Reproduction Toxicity Studies	**All regions:** A male fertility study should be completed prior to the initiation of Phase 3 trials **US:** Assessment of female fertility and embryo-fetal development should be completed before women of childbearing potential using birth control are enrolled in Phase 3 trials. **EU:** female fertility studies need to be completed prior to the initiation of Phase 3 trials **Japan:** assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial.
Repeated Dose Toxicity Studies	For the Phase III (Therapeutic Confirmatory) studies, the recommendations for the United States and Japan are the same as those in Table 1. In the EU, a 1-month toxicity study in two species (one rodent) would support clinical trials of up to 2 weeks duration (Table 2 below). Three month toxicity studies would support clinical trials for up to 1 month duration, while 6-month toxicity studies in rodents and 3-month studies in nonrodents would support trials of a duration up to 3 months. For longer term clinical trials, a 6-month study in rodents and a chronic study in nonrodents are recommended.

Table 2

Duration of Repeated Dose Toxicity Studies to Support

Phase 3 Trials in the EU and Marketing in All Regions*

Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
	Rodents	**Nonrodents**
Up to 2 Weeks	1 Month	1 Month
Up to 1 Month	3 Months	3 Months
Up to 3 months	6 Months	6 Months
> 3 months	6 Months	Chronic (footer)

*The above also reflects the marketing recommendations in the 3 regions except that a chronic nonrodent study is recommended for clinical use > 1 month.

The information presented in this table was taken directly from the FDA ICH M3, S1A, and S2B Guidance Documents

Summary of Nonclinical Safety Studies Needed Prior to Each Phase of Clinical Trials

STUDY TYPE	REQUIREMENT
For Marketing Approval	
Reproduction Toxicity Studies	In the three regions, the pre- and postnatal development study should be submitted for marketing approval or earlier if there is cause for concern. For all regions, all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control of whose pregnancy status is unknown.
Carcinogenicity Studies	When carcinogenicity studies are required they usually need to be completed before application for marketing approval. Completed carcinogenicity studies are not usually needed in advance of the conduct of clinical trials unless there is a cause for concern. Factors to consider for carcinogenicity testing follow: • Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months. For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. • Carcinogenicity studies may be recommended for some pharmaceuticals if there is a concern about their carcinogenic potential. • Assessment of genotoxic potential of a compound should take into account the totality of the findings and acknowledge the intrinsic value and limitations of both in vitro and in vivo tests. • Indication and patient population • The route of exposure in animals should be the same as the intended clinical route when feasible. • Extent of systemic exposure • Endogenous Peptides and Protein Substances or their Analogs For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing need not be conducted before market approval although these studies should be conducted post-approval In instances where the life-expectancy in the indicated population is short (i.e., less than 2-3 years), no long-term carcinogenicity studies may be required.

The information presented in this table was taken directly from the FDA ICH M3, S1A, and S2B Guidance Documents