

Nonclinical IND Studies to Support First-
In-Human Trials
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Nonclinical Studies to Support FIH Trials

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Nonclinical Studies to Support FIH Trials

- Regulations require an assessment of the safety and efficacy of human pharmaceuticals.
- Safety testing is conducted in animals to identify potential toxicities relevant to humans.



Nonclinical Studies to Support FIH Trials

–Types of FIH trials

- Often, FIH trials are acute-dose or short multiple-dose studies in healthy volunteers.
- For some indications, FIH trials may be longer-term multiple-dose trials in patients.

–IND applications

- Standard
 - Start dose selection
- Exploratory

–Nonclinical deficiencies resulting in clinical hold

–Case examples for FIH for rare disease



Nonclinical Studies to Support FIH Trials

- Importance of nonclinical studies
- Nonclinical studies to support more expanded FIH trials
- Nonclinical issues (e.g., patient population, biologics vs small molecules)
- Case examples for rare diseases
- Interactions with FDA



Investigational New Drug Applications (INDs)

- Standard IND
- Exploratory IND



Standard IND Application

21 CFR 312.23(a)(8): pharmacology/toxicology data for an IND.

- Pharmacology
- Safety Pharmacology
- PK/ADME
- Toxicology
- Genetic Toxicology



Standard IND Application

Nonclinical studies needed to support a first-in-human clinical trial:

Available pharmacology, PK/ADME data

Safety pharmacology (CNS, cardiovascular, respiratory)

Toxicology data

Toxicity studies in 2 species (rodent, non-rodent), up to a dose demonstrating overt toxicity, to a maximum feasible dose, or other appropriate criteria (e.g., limit dose or safety margin) and of a duration equal to or greater than that proposed clinically.



Standard IND Application

Toxicology studies (con't)

Expanded acute toxicity studies in rodent and non-rodent may be used to support an acute-dose study in humans

Genotoxicity studies

In vitro gene mutation in bacteria (Ames test)

In vitro cytogenetic assay in mammalian cells or in vitro mouse lymphoma tk assay (with colony sizing)



Considerations

- The need for nonclinical studies and/or the types of nonclinical studies needed may be modified under certain circumstances, including:
 - Serious and/or life-threatening indication
 - Relevant animal studies cannot be conducted
 - Limited clinical trial proposed



FIH Maximum Safe Starting Dose

- Selection of maximum safe starting dose for first-in-human trial (cf. Guidance for Industry: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers July 2005)
- Not intended to address dose-escalation or maximum clinical doses, or dosing in patient populations.
- Toxicity is to be avoided at the initial dose.
- Approaches other than that described may be used (e.g., PK/modeling); however, approach selected needs to be justified.



FIH Maximum Safe Starting Dose

- Identification of NOAEL in rodent and nonrodent
- Conversion of NOAELs to Human Equivalent Doses (using body surface area conversion factor)
 - BSA-CF: converts mg/kg dose in animals to mg/m² dose, then to mg/kg dose in human
- Selection of more sensitive species (i.e., lower HED)



FIH Maximum Safe Starting Dose

- Application of safety factor
 - default is 10, but may not be adequate in all cases
 - Increase
 - Steep dose-response curve
 - Severe toxicity at doses above NOAEL
 - Non-monitorable toxicities
 - Toxicities with no premonitory signs
 - Irreversible toxicity
 - Unexplained death
 - Widely variable bioavailability in animals
 - Non-linear PK
 - Wide variability between species in doses or exposures eliciting toxicities
 - Less than optimal nonclinical study design/conduct
 - Novel therapeutic targets
 - Animal models with limited utility



FIH Maximum Safe Starting Dose

- Application of safety factor
 - Decrease
 - Drug is a member of a well-characterized class, is being given according to an established clinical dosing regimen, and has similar PK/ADME and toxicity profiles across species, including human.
 - Toxicities are easily predicted, monitored, and are reversible.
 - Dose-response for toxicity is not steep.
 - The NOAEL upon which the HED is based was determined in longer-term nonclinical studies; this assumes that toxicities are cumulative and were not observed early in the longer-term studies.



FIH Maximum Safe Starting Dose

- It is always acceptable (from a safety perspective) to use a clinical start dose lower than the MRSD.
- Use of pharmacologically active dose (PAD)
 - May use if lower than MRSD
 - May be used to justify lowering the MRSD, e.g., in cases in which toxicity is due to exaggerated pharmacologic effects.



Exploratory IND Application

- IND for early clinical trials, typically first in human, using very small quantities of drug and involving very limited human exposure, with no intent to assess efficacy or to establish maximum tolerated doses in humans.
- Maybe be useful to investigate PK, PD biomarkers, receptor binding.
- Assumption that these types of clinical trials require less nonclinical data due to the reduced risk to humans compared to typical Phase 1 studies.



Exploratory IND Application

- Five different approaches ICH M3(R2); clinical dosing:
 - Approach 1: total dose $\leq 100 \mu\text{g}$ and total dose $\leq 1/100^{\text{th}}$ NOAEL and PAD (typically based on mg/m^2).
 - Approach 2: 5 doses of $\leq 100 \mu\text{g}$ each (total = $500 \mu\text{g}$ per subject) and each dose $\leq 1/100^{\text{th}}$ NOAEL and PAD (typically based on mg/m^2). $\geq 6 t_{1/2}$ washout between doses.
 - Approach 3: single dose at subtherapeutic dose or into the anticipated therapeutic range.
 - Approach 4-5: up to 14 days into therapeutic range, but not to MTD.



Exploratory IND Application

- Nonclinical studies needed for all approaches:
 - In vitro target/receptor profiling. Characterization of primary PD in a relevant model.
- General toxicity studies
 - Approach 1: expanded acute in one species (u. rodent), clinical or iv route. HD = 1000 fold clinical dose (mg/m^2) for oral.
 - Approach 2: 7-day repeat dose in one species (u. rodent), clinical or iv route, HD = 1000 fold clinical dose (mg/m^2) for oral.



Exploratory IND Application

- Approach 3: expanded acute in two species, clinical route, doses up to an MTD, MFD, or limit dose.
- Approach 4: 2-week in two species, doses selected based on exposure multiple of anticipated AUC at clinical HD.
- Approach 5: 2-week in rodent (justify use of rodent), doses up to an MTD, MFD, or limit dose; confirmatory study in non-rodent at NOAEL in rodent, ≥ 3 days, at least match clinical duration OR escalating dose in non-rodent, ≥ 3 days, at least match clinical duration.



Exploratory IND Application

- Genotoxicity studies

- Approach 1-2: none, but any studies or QSAR conducted should be submitted. For highly radioactive agents, need dosimetry.

- Approach 3: Ames assay (or other if Ames inappropriate)

- Approach 4-5: Ames assay and an in vitro or in vivo clastogenicity in mammalian system).



Exploratory IND Application

- Additional guidance on start and maximum clinical doses for Approaches 3-5 (refer to guidance).
- Other approaches might be acceptable, but should consult the appropriate review division for agreement.
- All nonclinical studies used to support studies under an exploratory IND must be conducted in compliance with GLP.



Exploratory IND Application

- Submissions need to be in accordance with FDA guidance, i.e., Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (Nov, 1995).
- After completion of proposed clinical trials, exploratory IND should be withdrawn and a traditional IND opened for the selected drug candidate.



Nonclinical Deficiencies Resulting in Clinical Hold

- Lack of studies
- Lack of adequate documentation (e.g., individual animal line listings)
- Inadequate doses (justification not provided)
- No no-effect dose for unacceptable toxicity
- Serious toxicity with no strategy for monitoring in humans
- Inadequate CIB



Use of Nonclinical Data

- IND X
 - Same product previously submitted to different division.
 - In initial submission, nonclinical studies identified severe clinical signs, including clonic convulsions, in both animal species.
 - Initial clinical trial allowed to proceed, but with a plasma exposure limit to avoid CNS toxicity in humans.



Use of Nonclinical Data

- IND Y
 - In the initial submission, evidence of neurodegeneration was observed in both animal species.
 - Clinical trial was allowed to proceed, but limited to a single dose in any individual subject until additional nonclinical data were provided.



Use of Nonclinical Data

- IND Z
 - In the initial submission, deaths reported in the non-rodent species; no premonitory signs or cause(s) of death established.
 - Clinical trial was allowed to proceed, but the highest proposed clinical dose was lowered to provide an acceptable safety margin.



FDA Guidances

- FDA guidances can be found at the following website:

<http://www.fda.gov/cder/regulatory/default.htm>

