Safety Considerations in Phase 1 Trials

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Learning Objectives

To understand:

- Important considerations in development prior to Phase 1 First-in-Human (FIH) trials
- Dose Selection for FIH Trials
- Safety considerations in conduct of FIH Trials

Outline

- General considerations in early clinical development of human drug products
- Objectives of Phase 1 Trials
- Considerations prior to First-in-Human (FIH) trials
- FIH Trials
  - Maximum Recommended Starting Dose (MRSD)
- Safety in FIH Trials
- BIA 10-2474: A Cautionary Tale
- Challenge Questions

General Considerations in Early Clinical Development of Human Drug Products

- Address uncertainty regarding potential benefits and risks of a new drug, including:
  - The mode of action of the new product
  - Availability of biomarkers (safety/efficacy)
  - Nature of the target
  - Relevance of available *in vitro* and animal studies
  - Characteristics of the population
    - healthy volunteers vs. patients
    - adults, pediatric patients, neonates, pregnant women, elderly
  - Potential genetic and phenotypic polymorphisms influencing PK and PD

Study design strategy should attempt to reduce uncertainties step by step

EMA 2017 Guidelines on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Objectives of Phase 1 Trials

- Explore safety and tolerability of the drug at intended doses
  - Dose-limiting adverse reactions
  - Maximum safe dose

- Pharmacokinetics (PK)
  - Drug metabolism/ADME
  - Possible accumulation of parent drug or metabolites
  - Drug-drug interactions
  - Food effect
  - Sub-populations with impaired elimination

- Pharmacodynamics (PD)

Types of Phase 1 Trials

- Single ascending dose (SAD) PK trials
- Multiple ascending dose (MAD) PK trials
- Drug-drug interaction studies (DDI)
- Bioavailability/Bioequivalence studies

Whom do Phase 1 Trials Usually Enroll?

- Healthy volunteers for FIH trials
- Specific populations (e.g. renal or hepatic impairment)
- Patients – if the drug is expected to be toxic

Safety of healthy volunteers or patients involved in Phase 1 trials is paramount!

Considerations Prior to FIH Trials: Animal Model Selection

Relevance of Animal Model in Comparison with Humans:

- Target expression, tissue distribution, primary structure
- PD
- PK/metabolism
- On/off target binding affinities and receptor/ligand occupancy
- Cellular consequences of target binding
- *In vitro* metabolic profile
- *In vitro* human cell systems or human-derived tissue

Considerations Prior to FIH Trials: Defining the Target

Nature of the target – beyond mode of action

- Biological function of the human target, potential downstream effects

- Potential polymorphism, homology, conservation of the target among animal species and humans

- Potential off-targets closely related structurally and functionally to the intended target

Considerations Prior to FIH Trials: Pharmacodynamics

Mechanism of action related to intended therapeutic use; interaction of the drug with intended and related targets

- *In vitro*
- *In vivo* using animal models SAD and MAD
- Previous clinical exposure with drugs of similar class or mechanism of action
- Type and “steepness” of dose-response relationship

Structure-Function Relationship: Quinolones

- Trovafloxacin – significant drug-related hepatic toxicity and necrosis seen post-market
- Temafloxacin – severe hemolysis, renal failure, hepatic dysfunction
- Both drugs share an unique difluorinated side chain not found in other quinolones (e.g. ciprofloxacin, levofloxacin) that renders the drug highly lipophilic

Considerations Prior to FIH Trials: Additional Nonclinical Data

- Safety pharmacology and toxicokinetic data needed in all species utilized in nonclinical studies

- Toxicology
  - Exaggerated pharmacological actions?
  - Do target organs identified in non-clinical studies warrant special clinical monitoring?
  - Follow-up studies when serious toxicity or death is observed
  - Some serious toxicities translate poorly to humans (immune rx with monoclonal antibodies

Limitations of Nonclinical Studies

- Human bioavailability and metabolism may differ significantly from that of animals
- Mechanisms of toxicity may be unknown
- Toxicity may be due to an unidentified metabolite, not the parent drug

Unexpected Toxicity - Example

Drug A – dihydrofolate reductase inhibitor antibacterial drug with PO and IV formulation

- Nonclinical studies in rats, marmosets, rabbits and minipigs
- IV formulation: no liver findings on gross and histopathology
- PO formulation: occasional AST/ALT elevation, increased liver weights, hepatocellular hypertrophy, 1 marmoset with focal necrosis

Human Phase 1 (oral):

- Extreme elevations in AST/ALT in MAD;
- Delayed onset of liver damage and long-term persistence of injury; 1 patient with hepatic necrosis.
- Development of oral form abandoned

First-in-Human Trials

Establishing the Maximum Recommended Starting Dose (MRSD)

- Relevant nonclinical data
  - Pharmacologically active dose
  - Toxicologic profile of the compound
  - ADME (absorption, distribution, metabolism, excretion)
  - Exposure-effect relationships

- Clinical data (PK, PD, Adverse events, tolerability) from early cohorts

- Nonclinical and clinical experience with drugs with similar modes of action

Selecting the MRSD

- No Observed Adverse Effect Levels (NOAEL) in tested animal species
- Conversion of NOAEL to Human Equivalent Dose (HED)
- Selection of most appropriate animal species
- Application of a safety factor

Selecting the MRSD

- Algorithm for systemically administered drugs
- Topical, intranasal, compartmental administration routes and depot formulations can have additional considerations
- Data such as exposure/toxicity relationships, pharmacologic data or prior experience with related drugs can affect the choice of most appropriate species, scaling and safety factors

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Step 1: Determine NOAEL

Step 2: Convert NOAEL to HED

Step 3: Select HED from most appropriate species

Step 4: Divide HED by Safety Factor

Maximum Recommended Starting dose

Consider lowering dose based on PAD

NOAEL Determination

NOAEL – the highest dose level that does not produce a significant increase in biologically significant adverse events in comparison to the control group.

- Benchmark for safety
- A starting point for determining a safe starting dose for new molecular entities (NME) in healthy volunteers

Do NOT confuse with:

- NOEL (No Observed Effect Level)
- LOAEL (Lowest Observed Adverse Effect Level)
- MTD (Maximum Tolerated Dose)

NOAEL Determination

Three types of findings:

- Overt toxicity (clinical signs, micro- and macroscopic lesions)
- Surrogate markers of toxicity (serum liver enzyme levels)
- Exaggerated PD effects

General Rule: an adverse event (AE) observed in nonclinical studies for the purpose of dose-setting should be based on an effect that would be unacceptable if produced by the initial dose of a drug in a Phase 1 trial in healthy humans

Human Equivalent Dose Calculation

- NOAEL→ HED conversion is usually based on normalization of doses to body surface area

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

Selection of Most Appropriate Animal Species

- The most sensitive species generates the lowest HED, i.e. the most conservative starting dose

- If a particular animal species is most appropriate to assess human risk, the HED for that species is used regardless of whether it is the most sensitive species

- A species may be an inappropriate toxicity model if the dose-limiting toxicity in that species had limited value for human risk assessment

Application of a Safety Factor

- Determine the HED of a NOAEL in the most appropriate species, then apply a safety factor to provide a margin of safety for human volunteers

- Allows for:
  - Enhanced sensitivity in humans to the toxicity associated with a drug
  - Varied bioavailability across species
  - Difficulties detecting certain toxicities in animals e.g headaches/myalgias
  - Differences in receptor densities or affinities
  - Interspecies differences in ADME
  - Unexpected toxicities

- HED/Safety factor (at least 10) = MRSD (mg/kg)

Is a Safety Factor of 10 Always Appropriate?

Consider increasing the safety factor if:

- Steep dose-response curve
- Severe toxicities
- Nonmonitorable toxicity e.g. histopathologic changes
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large variability in doses or drug levels that elicit an effect
- Nonlinear PK
- Novel therapeutic targets
- Animal models with limited utility

Is a Safety Factor of 10 Always Appropriate?

Consider decreasing the safety factor if the drug:

- Is a member of a well-characterized class – and administered by the same route, schedule and duration of administration
- Has similar metabolic profile and bioavailability
- Has similar toxicity profiles across all species tested including humans
- Toxicities are easily monitored, reversible, predictable with a relatively shallow dose-response relationship and toxicities that are consistent across species

Consideration of a Pharmacologically Active Dose (PAD)

- For certain classes of drugs or biologics, e.g., vasodilators, anticoagulants, monoclonal antibodies, toxicity may arise from exaggerated pharmacologic effects

- In these cases, the PAD may be a more sensitive indicator of potential toxicity than the NOAEL and may warrant lowering the MRSD.

MRSD Calculation – Example 1

- HED derived from rats was ~400 mg
- Starting dose of 100 mg was proposed (safety factor of 4)
- Rationale:
  - Member of a well-characterized class of drugs
  - Toxicity studies in both rats and monkeys were significantly longer duration than the proposed clinical trial
  - Potential toxicities were readily monitorable and reversible

MRSD Calculation – Example 2

- HED derived from NOAEL in rats ~ 400 mg
- Starting dose of 20 mg (safety factor of 20) was proposed
- Rationale:
  - More toxicity observed in animals at doses higher than 400 mg in comparison to other members of the same drug class
  - Neurological toxicity: potentially irreversible, difficult to monitor
  - Bioavailability in animals was low – might be higher in humans

Safety in FIH Trials: Dosing

- Ideally, a single subject should receive a single dose, then sequential administration within each cohort
- Adequate observation period between dosing to observe and interpret adverse reactions
- Duration of observation will depend on product properties and PK/PD characteristics
- If AE is delayed, repeated administration of drug can lead to cumulative toxicity

Safety in FIH Trials: Dose Escalation

- Is the dose escalation schedule appropriate?
  - Maximum fold increase in dose/exposure
  - Number of cohorts
  - Caution if small therapeutic window seen in nonclinical data, poor animal models or concerns about toxicity
  - Guided by dose-response for efficacy and safety in nonclinical studies

- Is the period of observation and follow-up before each dose escalation appropriate?

- Linear vs. non-linear PK?

Safety in FIH Trials: Maximum Exposure

- Should be pre-defined in the protocol and justified based on all prior data
- Is target saturation a factor? No further therapeutic effect expected despite increase in dose
- Maximum tolerated dose (MTD) may be defined for trials involving patients with consideration of risk/benefit.
- Trial design using MTD is not appropriate for healthy volunteers

Safety in FIH Trials: Single to Multiple Dosing

- PK/PD parameters, nonclinical safety data, single dose cohorts, linear vs. non-linear PK; half-life vs. duration of action, potential for accumulation
- Duration of multiple dose studies should be based on duration of nonclinical studies
- Generally, repeat-dose toxicity studies in 2 species (one non-rodent) for a minimum of 2 weeks supports a clinical trial up to 2 weeks in duration
- Route and rate of administration

FIH Trial Conduct – Choice of Subjects

- Do the foreseen toxicities justify the inclusion of healthy volunteers?
- Relative presence of drug targets in healthy subjects vs. patients
- Possible interactions with subject's lifestyle – smoking, drugs, alcohol
- Use of concomitant medications
- Special populations i.e. extremes of age, gender, ethnicity, genotypes

Safety Monitoring

- Define safety assessments – timing, additional monitoring, interventions according to pharmacological effects/nonclinical profile
- Clear plan to monitor AEs and train staff to recognize and respond
- Routine general monitoring – vital signs, ECG, lab values, physical exam for unexpected AEs
- Frequency of monitoring – need for more frequent observation within the first week after dosing; more frequent clinic visits and lab follow-up for subjects with AEs or lab abnormalities

Safety Monitoring

- Duration of monitoring – long enough to preclude risk of undetected serious toxicity

- Duration of clinical observation should be adequate for the condition being studied, study objectives and endpoints and expected response to product

- Precautions when treating subjects within a cohort and between cohorts

Safety Monitoring: Labs/Facilities

Laboratory test data should be appropriate and adequate:

- Routine assessment of all organ systems?
- Sufficiently detailed to characterize expected target organ toxicities?
- Stopping rules for patients whose laboratory test abnormalities reach a certain threshold?

Facilities:

- Controlled conditions/inpatient care
- Close supervision
- Capabilities for resuscitation in emergency situations
- Availability of hospitals nearby

Safety Monitoring: Stopping Rules

Clear stopping rules must be established for stopping the drug, stopping enrollment, stopping dose escalation, termination of the trial

Protocol changes for observed toxicity; List of “acceptable” toxicities

For healthy volunteers

- A serious adverse event related to the drug in one subject
- Severe non-serious AE in 2 subjects in the same cohort

Safety Reporting

Final Rule for IND Safety Reporting Requirements – 21 CFR 312 and 320

21 CFR 312.32(a)

- Adverse event
- Life-threatening AE or life-threatening suspected AE
- Serious AE or serious suspected AE
- Suspected AE
- Suspected Unexpected Serious Adverse Reactions (SUSARs) expedited reporting to investigator, ethics committees, agencies

Formulate a clear plan for prompt communication among multiple study sites!

BIA 10-2474: A Cautionary Tale

- Oral fatty acid amide hydrolase (FAAH) inhibitor for treatment of neuropathic pain.
- Nonclinical trials done in mice, rats, dogs and monkeys
- Phase 1 trial:
  - SAD - 64 volunteers received single 0.25 to 100 mg doses of the drug. No serious AEs
  - MAD - Dose range: 2.5 mg-50 mg daily for 10 days. Eight subjects per dose cohort (6 drug, 2 placebo)
    - 2/6 in 10 mg group with blurry vision

BIA 10-2474: A Cautionary Tale

- MAD
  - 6 of 8 healthy men (ages 28-49) in the 50 mg cohort received active drug almost simultaneously
  - Day 5/10 - subject 1 was hospitalized with headache and blurry vision
  - Day 6/10 - subjects 2-6 were given study drug; 4/5 were hospitalized with similar symptoms
  - Subject 1 died; the other 4 suffered brain damage

What went wrong?

- FAAH enzyme inhibition was prolonged
- Cumulative toxicity with multiple doses
- Off-target inhibition of other proteins?
- Lack of dosing interval between consecutive subjects
- Lack of communication with other trial participants and investigators

Challenge Question #1

Which of the following is used to calculate the MRSD?

a) NOAEL
b) LOAEL
c) MTD

Challenge Question #2

If a new drug has a steep dose-response curve and serious toxicity in animal models, the safety factor used to calculate the MRSD should be greater than 10.

a) True
b) False

References

- Draft ICH Harmonised Guideline: General Considerations for Clinical Studies E8(R1); May 2019

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies

- Guidance for industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf
- Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf
- Guidance for industry: S7A Safety pharmacology studies for human pharmaceuticals
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformatio n/Guidances/ucm074959.pdf
- Singh H et al. French Phase 1 Clinical Trial Disaster: Issues, learning points and potential safety measures. J Nat Sc Biol Med 2018; 9:106-10
- https://www.sciencemag.org/news/2016/02/french-company-bungled-clinical-trial-led-death-and-illness-report-says


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