Safety Considerations in Phase 1 Trials

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Outline

• General considerations for Phase 1 trials
  – Objectives, types of trials, subjects

• First in Human studies
  – Key considerations
  – Starting dose
  – Safety factor

• Safety monitoring
  – Stopping rules, safety reporting

• Predictable and unpredictable adverse events
General Considerations

• Objectives
  – Assess safety
  – Evaluate pharmacokinetics and pharmacodynamics
  – Explore drug metabolism and drug interactions

• Types of Phase 1 trials
  – Single ascending dose pharmacokinetic trials
  – Multiple ascending dose pharmacokinetic trials
  – Exposure-response studies
  – Drug interactions
  – Bioavailability/Bioequivalence studies
General Considerations

• Phase 1 Subjects
  – Usually healthy volunteers
  – Patients are enrolled when drug is known or expected to have toxicities
    • cytotoxic agents, biological agents
  – Specific populations (elderly, renal or hepatic impairment)
First in Human Trials

Before proceeding with First in Human trials, consider evidence from non-clinical studies with respect to:

– Characteristics of the test drug (biologic, long half-life)
– Duration and total exposure proposed in humans
– Disease targeted for treatment
– Populations in which drug will be used
– Route of administration (systemic, topical)
First in Human Trials

Non-clinical animal studies should provide sufficient safety support for the proposed clinical trials

- Choice or relevance of the animal species
- Identifying potential target organs of toxicity
- Duration, dose, route of exposure
- Pharmacokinetic and pharmacodynamic assessments
- Identifying dose response
- Safety in special populations (pediatrics, pregnant women)
First in Human Trials

Questions to Consider:

– Is the proposed starting dose appropriate?
– Is the dose escalation scheme, dose increment, and amount of information before escalation appropriate?
– Are the sample sizes appropriate for each dose escalation?
– What is the quality of the investigational product (Chemistry, Manufacturing, and Controls)
– Are the clinical trial protocols designed appropriately to ensure safety and meet objectives?
First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

• Steps in selecting MRSD:
  – Determination of no observed adverse effect level (NOAEL) in the tested animal species
  – Conversion of NOAELs to human equivalent dose (HED)
  – Selection of the most appropriate animal species
    • In the absence of data on species relevance, the most sensitive species is chosen (i.e. the species in which the lowest HED can be identified)
  – Application of a safety factor
First in Human Trials

Starting Dose (MRSD)

• Application of the safety factor
  – The default safety factor is usually 10-fold lower NOAEL HED
  – Allows for variability in extrapolating from animal toxicity studies to studies in humans
    • Differences in receptor densities or affinities
    • Interspecies difference in absorption, distribution, metabolism, excretion (ADME)
  – Uncertainties due to enhanced sensitivity in humans vs. animals
  – Difficulty in detecting certain toxicities in animals (headache)
  – Unexpected toxicities
First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

• Increasing the safety factor to greater than 10-fold
  – Novel therapeutic class
  – Severe, irreversible, or toxicities that are not easily monitored
  – Non-linear pharmacokinetics: limits the ability to predict dose-related toxicity
  – Variable bioavailability in animals might underestimate toxicity
  – Sequential enrollment of study subjects

• Decreasing the safety factor to less than 10-fold
  – Members of a well-characterized class
  – Easily monitored, reversible, predictable toxicities
  – NOAEL based on toxicity studies of longer duration

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STEP 1: Determine NOAEL

STEP 2: Convert each animal NOAEL to HED

STEP 3: Select HED from most appropriate species

STEP 4: Choose safety factor and divide HED by that factor

Maximum recommended starting dose (MRSD)

STEP 5: Consider lowering dose based on other factors
First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

• Example 1 of safety factor greater than 10-fold
  – HEDs derived from NOAEL in rats was ~ 400 mg
  – Starting dose of 20 mg was proposed
    • Safety factor of 20
  – Rationale provided
    • More toxicity was observed in animals (doses higher than 400 mg) in comparison to members of the drug class from which it was derived
    • Neurological toxicity: potentially irreversible and difficult to monitor
    • Bioavailability was low in animals – human exposure could be higher
First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

• Example 2 of safety factor less than 10-fold
  – HEDs derived from NOAEL in rats was ~ 400 mg
  – Starting dose of 100 mg was proposed
    • Safety factor of 4
  – Rationale provided
    • member of a well-characterized class of drugs
    • toxicity studies in both rats and monkeys were of appreciably longer duration than the proposed clinical trial
    • potential toxicities were able to be monitored and reversible
First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

• Example 3 of poor study design: lack of sequential enrollment
  – Novel biologic drug intended to treat a serious disease
  – There were animal toxicology findings of concern, starting dose safety factor greater than 10-fold
  – Drug administered simultaneously to healthy volunteers at a clinical trials unit
  – All 6 healthy volunteers became acutely ill and within hours were hospitalized with multi-organ failure, ICU admissions
First in Human Trials

Dose Escalation

• The time course of potential adverse event(s) is unknown
• Cautious incremental rate of dose escalation
  – small therapeutic window seen in preclinical data
  – animal models don’t predict human experience
  – toxicity concerns
  – when the adverse event is delayed
• Advancing to multiple ascending dose, duration of multiple dose studies should be based on duration of nonclinical animal toxicology studies
Safety Monitoring in Phase 1 Trials

General Approaches

• Appropriate monitoring scheme to monitor for clinical signs or symptoms of adverse events likely to be associated with the drug

• Stopping rules for administering the drug, stopping enrollment, and stopping dose escalation

• Duration of clinical observation should be adequate with respect to
  – stated objectives and endpoints
  – the anticipated response to product
  – health-related conditions being studied
Safety Monitoring in Phase 1 Trials

• Frequency of monitoring
  – Need for more frequent observation within the first week following initial dosing
  – More frequent clinic visits for subjects found to have developed adverse events or laboratory abnormalities
  – Follow up should be long enough to preclude the possibility of undetected serious toxicity
  – Sometimes need for prolonged observation of the subject in a hospital setting following initial dosing
Safety Monitoring in Phase 1 Trials

- Laboratory test data collected should be appropriate and adequate
  - Do they include routine assessment of all organ systems?
  - Are they sufficiently detailed and complete for organs more likely or known to be affected by the agent?
  - Are there stopping rules for patients whose laboratory test abnormalities reach a certain threshold?
Safety Monitoring in Phase 1 Trials

Stopping Rules

• Protocol-defined rules to halt study drug administration and/or halt enrollment of additional subjects
  – Based on observed adverse event of greater severity
    • Can be self-evident but toxicity grading scales are helpful!
  – Observe study subject until adverse event has resolved
  – Review safety data in all prior subjects
  – Careful evaluation of all safety data
  – Then resume the study with or without protocol changes
  – FDA informed of every step – may impose “clinical hold”
Example of Predictable Toxicities

• Linezolid:
  – Antibacterial drug
  – New member of the oxazolidinone class
  – Activity against Gram positive organisms including some resistant organisms

• Myelosuppression noted in non-clinical toxicology studies
  – bone marrow hypocellularity
  – decreased extramedullary hematopoiesis
  – decreased levels of circulating erythrocytes, leukocytes, and platelets

• Clinical development pursued because of its potential for therapeutic benefit
Example of Predictable Toxicities

Linezolid:
• Phase 1: careful monitoring of CBC – no concerns
• Phase 3 trials: thrombocytopenia observed in a few patients
• At the time of initial approval the package insert included:
  – PRECAUTIONS section had information about development of thrombocytopenia
  – Pharmacology section: hematopoietic effects noted in animals
• Post-marketing: Myelosuppression including leukopenia, anemia, pancytopenia, as well as thrombocytopenia
  – Package insert updated WARNING regarding myelosuppression

Linezolid label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021130s037,021131s030,021132s035lbl.pdf
Example of Predictable Toxicities

Telavancin: Lipoglycopeptide antibacterial; effective against MRSA

- Non-clinical studies: Renal tubular vacuolization, renal tubular degeneration, elevations of BUN/serum creatinine
- Phase 3 trials: decreased efficacy/mortality in patients with renal impairment; nephrotoxicity more common in telavancin-treated patients
- Package Insert:
  - Boxed Warning, Warnings and Precautions
  - Animal Toxicology and/or Pharmacology

Telavancin label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022110s012lbl.pdf
Example of Predictable Toxicities

Hypothetical example of Drug A

- Member of a known class of drugs that has been associated with hepatotoxicity
- Studies initiated at smaller dose (MSRD greater than 10-fold NOAEL HED) with evaluation of safety data in each cohort prior to dose escalation
- Hepatotoxicity was noted during dose escalation in the second dose cohort prior to reaching the targeted dose
- Further development not pursued
Example of Unpredictable Toxicities

Hypothetical example of Drug B

• Member of a drug class with the FDA-approved drugs considered to be well-characterized: safe and effective

• New drug B: structure modified to enhance spectrum of activity
  – No unusual toxicities seen in animal studies: NOAEL established
  – Proceeded to Phase 1 trials
    • Single-dose well tolerated
    • In multiple-dose Phase 1 trials, subjects developed moderate-severe skin reactions: stopping rule met! Hypersensitivity reactions
  • Product development halted
Safety Reporting

• Reporting requirements
  – 21 CFR 312.32: “IND Safety Reporting”

• Definitions: 21 CFR 312.32(a)
  – Adverse event: any untoward medical occurrence
  – Life-threatening adverse event or life-threatening suspected adverse reaction
  – Serious adverse event or serious suspected adverse reaction
  – Suspected adverse reaction
  – Unexpected adverse event or unexpected suspected adverse reaction
Summary of Phase 1 Trials

• Overview of safety in phase 1 trials
  – Important considerations prior to dosing in humans
• Safe starting dose in humans
  – Examples of MRSD calculation; safety factor
• Safety monitoring, stopping rules, safety reporting
• Relevance of toxicities in non-clinical studies to adverse events in humans
  – Examples of predictable and unpredictable toxicities
References

• ICH E8: General considerations for clinical trials.

• Guidance for industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers.

• Guidance for industry: S7A Safety pharmacology studies for human pharmaceuticals.

• Guidance for industry and investigators safety reporting requirements for INDs and BA/BE studies

• Guidance for industry: Toxicity grading scale for healthy volunteers