



Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

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de santé et des aliments



Session 6 –Clinical Trial Assessment Phase I Clinical Trial

**Presentation to APEC Preliminary Workshop
on Review of Drug Development
in Clinical Trials**

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Slide 1

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop

Overview

- Characteristics of Phase I trials
- Core preclinical requirements
- Considerations for biologics
- Considerations for first-in-human
- Preclinical testing of cytotoxic/cytostatic drugs
- Phase I in Oncology, HIV/AIDS, Allergic Rhinitis/Asthma/COPD
- Approaches in protocol and informed consent review
- Common deficiencies
- Exercises

Characteristics of Phase I Trials (1)

- Subject population: healthy volunteers but for higher risk / potentially toxic drug products such as in oncology or most biologics, patients are recruited
- Sample size typically around 20
- Single-dose escalation or repeat-dose range or escalation
- Randomized double-blind parallel group or cross-over
- Single arm, proof-of-concept
- Thorough QT/QTc studies

Characteristics of Phase I Trials (2)

- Endpoints:
 - Safety, including effects on QT/QTc interval
 - MTD and recommended Phase II dose (RP2D)
 - PK/PD (AUC_t , C_{max} , T_{max} , vs PD markers)
 - Bioavailability
 - Metabolism and elimination (elimination half-life)
 - Drug and food interactions
 - Formulation testing / bioequivalence

Goals of Preclinical Safety Evaluation

- The primary goals of preclinical safety evaluation are (ICH S6):
 - 1) to identify an initial safe dose and subsequent dose escalation schemes in humans
 - 2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible
 - 3) to identify safety parameters for clinical monitoring

Core Toxicity Evaluation (1)

- For single-dose phase I and repeat-dose phase I studies of up to 14 days duration:
 - ADME/toxicokinetics in rodent and non-rodent animal species
 - Safety pharmacology (cardiovascular, CNS, respiratory – ICH S7A)
 - Non-clinical evaluation of the potential for QT-prolongation (ICH S7B)
 - Single-dose in 2 mammalian species (ICH M3)
 - 14-day repeat-dose in rodent and non-rodent animal species (ICH M3)

Core Toxicity Evaluation (2)

- Genotoxicity studies (ICH S2B):
 - A test for gene mutation in bacteria
 - An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells **or** an *in vitro* mouse lymphoma tk assay
 - An *in vivo* test for chromosomal damage using rodent hematopoietic cells

Core Toxicity Evaluation (3)

– Reproductive toxicity studies (ICH M3):

- Male and female reproductive organs should always be evaluated in the repeated-dose toxicity studies
- 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
- EU - assessment of embryo-fetal development should be completed prior to Phase I trials in women of childbearing potential and female fertility studies prior to Phase III trials

Core Toxicity Evaluation (4)

- Reproductive toxicity studies (ICH M3, continued):
 - US & Canada - women of childbearing potential may be included in early, carefully monitored studies without reproduction toxicity studies provided appropriate precautions are taken to minimise risk (male and female reproductive organs are evaluated in repeated-dose toxicity studies)
 - Pregnant women - Prior to the inclusion of pregnant women in clinical trials, all the reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted, and safety data from previous human exposure are generally needed

Core Toxicity Evaluation (5)

- Local tolerance: assessment of local tolerance may be part of other toxicity studies

Considerations for Biologics (1)

ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- Specifications of test material:
 - It is preferable to rely on purification processes to remove impurities and contaminants rather than to establish a preclinical testing program for their qualification
 - The product should be sufficiently characterised to allow an appropriate design of preclinical safety studies
 - In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies

Considerations for Biologics (2)

- **Preclinical safety testing should consider:**
 - selection of the relevant animal species
 - age
 - physiological state
 - the manner of delivery, including dose, route of administration, and treatment regimen
 - stability of the test material under the conditions of use

Considerations for Biologics (3)

- Safety evaluation programs should normally include two relevant species
- A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)
- Sample size adequate to assess potential toxicity; frequent and prolonged monitoring (e.g., when using non-human primates)

Considerations for Biologics (4)

- Measurement of antibodies should be performed when conducting repeated dose toxicity studies
- The effects of antibody formation on PK/PD parameters, incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered
- Attention should also be paid to the evaluation of possible pathological changes related to immune complex formation and deposition

Considerations for Biologics (5)

- Standard battery of genotoxicity studies generally not applicable
- Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals
 - To explore carcinogenic potential, may use malignant and normal cell lines
 - When *in vitro* data give cause for concern about carcinogenic potential, further studies in relevant animal models may be needed

Preclinical Testing for Cytotoxic/Cytostatic Drugs (1)

EMA: Note for guidance on the pre-clinical evaluation of anticancer medicinal products

Drug Activity:

- In vitro activity profile on panel of cell lines
- In vivo animal tumour model

Evaluate Toxicity:

- To establish the MTD to be used to define the starting dose in Phase I
- To identify effects on vital functions and target organ toxicity in relation to drug exposure and “treatment cycles” to support dose escalation in Phase I studies and duration of therapy

Preclinical Testing for Cytotoxic/Cytostatic Drugs (2)

- Safety pharmacology for compounds with a novel mechanism of action
- Single-dose studies in mice and rats to determine MTD
- Repeated-dose toxicity study of limited duration (2 to 4 weeks or 1 to 2 cycles) in two rodent species to assess target organ toxicity and reversibility of effects
- Rodent and non-rodent for drugs with novel mechanism of action
- Genotoxicity/carcinogenicity not required prior to Phase I and II
- Reproduction toxicity studies not required
- Local tolerance

Considerations for FIH (1)

- **EMA guidance:** Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
- Factors of risk may include the drug's mode of action, the nature of the target, and/or the relevance of animal models:
 - Mode of action on **multiple signalling pathways** or targets that are expressed in many tissues
 - **Amplification** of an effect that might not be sufficiently controlled by a physiologic feedback mechanism (e.g., immune system; blood coagulation system)

Considerations for FIH (2)

Factors of risk (continued)

- Insufficient knowledge on the structure, tissue distribution (including expression in immune cells), cell specificity, disease specificity, regulation, level of expression, and biological function of the **human target** including “down-stream” effects, and how it might vary between individuals in different populations of healthy subjects and patients
- Insufficient information on **polymorphisms** of the target in relevant animal species and humans, and the impact of polymorphisms on the pharmacological effects of the medicinal product

Considerations for FIH (3)

Factors of risk (continued)

- **Questionable relevance** of animal species/models or surrogates for thorough investigation of the pharmacological and toxicological effects of the medicinal product
- **Quality aspects:** determination of strength and potency; qualification of material used; reliability of very small doses
- **If factors of risk identified**, should estimate the starting dose in humans using the Minimal Anticipated Biological Effect Level (MABEL) in addition to the NOAEL

Considerations for FIH (4)

- Study protocol should be designed to mitigate risk factors, with consideration given to the following aspects:
 - Study population
 - Trial site
 - First dose
 - Route and rate of administration
 - Number of subjects per dose increment (cohort)
 - Sequence and interval between dosing of subjects within the same cohort
 - Dose escalation increments
 - Transition to next dose cohort
 - Stopping rules
 - Allocation of responsibilities for decisions with respect to subject dosing and dose escalation

Starting dose (1)

- **FDA Guidance for Industry:** Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (mainly for systemic therapies)
- **Scaling factors used to convert NOAEL in each species tested to a human equivalent dose**
- **Safety margin of at least 10 should be considered (HED/10)**
- **Starting dose in FIH using patients is dependent on many factors: patient population, disease, animal PK or PK/PD, animal dose-toxicity data, or other non-clinical data**

Starting dose (2)

Other common methods to determine the starting dose:

- The similar drug approach that may be used when clinical data are available for another compound of the same chemical class as the investigational drug
- The pharmacokinetically guided approach that uses systemic exposure rather than dose for the extrapolation from animal to man
- The comparative approach that consists of utilizing two or more methods to estimate a starting dose and then critically comparing the results to arrive at the optimal starting dose

(Eur.J.Clin.Pharmacol. V.57:835-845, 2002)

Phase I in Oncology (1)

Objectives of Phase 1 oncology trials

- Evaluate safety and tolerance
- Determine dose-limiting toxicity
- Define maximum tolerated dose
- Define optimal biologically active dose
- Determine dose and schedule for initial Phase II efficacy trials
- Evaluate pharmacokinetics (ADME)
- Evaluate effects on molecular target or pathway
- Observe for preliminary evidence of antitumour activity

(Br J Clin Pharmacol. 2006 July; 62(1): 15–26)

Phase I in Oncology

- Goal is to escalate to the MTD rapidly, but safely, to minimize the likelihood of treating patients at doses that are too low to yield benefit or too high that they do harm

Phase I in Oncology (2)

- Approaches to determine starting dose:
 - 1/3 of the toxic dose low (TDL) in a large animal species (TDL = the lowest dose that produces drug-induced pathological alterations in hematological, chemical, clinical, or morphological parameters and which, when doubled, produces no lethality)
 - 1/10 of lethal dose in mice (expressed in mg/m^2) if nontoxic in large species

Dose-Escalation Methods (1)

- Modified Fibonacci sequence (100%, 67%, 50%, 40%, and 33%), where 3 patients treated per cohort
- Target dose-limiting toxicity rate (e.g., 33%, 50%) chosen based on whether or not the drug has potential for unpredictable, irreversible, or life-threatening toxicity
- DLT = consists of serious or life-threatening side effects, but reversible
- Escalation methods are “adaptive”

Dose-Escalation Methods (2)

- **For toxicity rate of 33%:**
 - If 0/3 patients has DLT, then escalate
 - If 2/3 or 3/3 patients have DLT, then escalation stops and the current dose is the MTD
 - If 1/3 patients has DLT, then 3 additional patients are treated; the dose is escalated only if none of the 3 additional patients has DLT

MTD = dose at which ≥ 2 patients experience DLT

RP2D = next lower dose at which no more than 1/6 patients has DLT

Dose-Escalation Methods (3)

- **For toxicity rate of 50%:**
 - If 0/3 patients has DLT, then escalate
 - If 3/3 patients have DLT, then escalation stops, and the current dose is the MTD
 - If 1/3 or 2/3 patients has DLT, then 3 additional patients are treated. The dose is escalated only if $\leq 2/6$ patients have dose-limiting toxicity

MTD= dose at which ≥ 3 patients experience DLT

RP2D= next lower dose at which $\leq 2/6$ patients have DLT

Dose-Escalation Methods (4)

- Bayesian methods where set of prior information and data on each subject is taken into consideration in deciding the dose for the next subject
- For newer targeted therapies, goal may be to determine the biological effect level rather than the MTD

Dose-Escalation Methods (5)

- Dose-limiting toxicities should be defined
 - Specific toxicities may be defined based on the known toxic effects of the drug (e.g., haematological toxicity) and/or
 - Defined as any toxicity of a pre-defined threshold grade
 - Grading of toxicities must be based on an established toxicity scale such as the NCI CTCAE v.3

Phase I Studies in HIV/AIDS

- Single-dose and repeated-dose, double-blind, placebo-controlled studies in healthy volunteers, to investigate:
 - Safety and PK
 - PK profile is very important, including terminal half-life and C_{min} to determine dosing
 - Food-effect and drug-drug interactions
 - Thorough QT/QTc
- Phase I studies in patients where drug is known to be too toxic for healthy volunteers or if the drug is considered high risk (e.g., biologics, immune system as the target)

Phase I Studies in Allergic Rhinitis, Asthma or COPD

- Single and repeated-dose in healthy volunteers to examine safety, PK, and potential efficacy by examining PD endpoints in controlled-environment studies of ozone challenge model for COPD
- Single and repeated-dose in atopic patients to examine safety, PK, and potential efficacy by examining PD endpoints in controlled-environment studies of allergen inhalation challenge (allergic rhinitis, asthma, COPD)

Approach in Review

- Benefit / risk judgement call:
 - Lower risk products → healthy volunteers
 - Higher risk products → patients
 - Potential toxicity with drug target (e.g., immune system, coagulation pathway)
 - Route of administration
 - Adequacy of pre-clinical program
 - Extent of toxicological findings
- Regardless of study population, always link the nonclinical toxicological findings to the clinical safety assessments

Protocol Assessment (1)

- Background and Rationale
- Trial Objectives
- Study Design and Duration
- Study Site(s)
- Sample Size
- Subject Population

Protocol Assessment (2)

- Eligibility Criteria
- Drug Formulation and Dosages
- Pre-study Screening and Baseline Evaluation
- Treatment / Assessment Visits
- Concomitant Medication

Protocol Assessment (3)

- Rescue Medication & Risk Management
- Premature Withdrawal / Discontinuation Criteria
- Efficacy Variables and Analysis
- Safety Variables and Analysis

Informed Consent Assessment (1)

- Ensure that the informed consent form explains:
 - The objectives of the trial and that it involves research
 - That there are no benefits to healthy volunteers and/or no anticipated benefits to patients
 - That the drug has never been administered to humans before (if applicable) or describes all previous studies in humans
 - The preclinical toxicity findings and potential adverse events for the drug, including any information on the drug's teratogenicity and the importance of contraceptive precautions

Informed Consent Assessment (2)

- Ensure that the informed consent form explains:
 - All the tests and procedures related to the trial, including duration of visits, overnight stays
 - The total amount of blood taken and provides a comparison measure such as a standard blood donation
 - Clearly informs subjects of their rights, that their enrolment in the trial is voluntary and they are free to withdraw from the study at any time
 - That their medical records may be accessed by the regulator mandated to oversee clinical trials

Common Deficiencies of Phase I Proposals

- Insufficient pre-clinical data
- No animal model or, for immunological reasons, data in animals is unreliable
- Healthy volunteers vs. patients
- Due to lack of resources, sponsors just want to try a study in humans “to get some human data”
- Previous human data is from completely different patient population and sponsor lacks pre-clinical animal model



References

EMA FIH	http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf
EMA Oncology	http://www.emea.europa.eu/pdfs/human/swp/099796en.pdf
FDA FIH healthy volunteers	http://www.fda.gov/cder/guidance/5541fnl.pdf
Clinical PSEAT	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/pseat_cta_meiep_dec_e.pdf