Federal **A**gency for **M**edicines and **H**ealth **P**roducts
(FAMHP)

Initial clinical trial protocol design considerations

Walter Janssens
Coordinator Early Phase Development

28.05.2010

Elements of the clinical trial protocol

- CPMP/ICH/135/95 (ICH E6)
- General information
- Background information
- Trial objectives
- Trial design
- Selection and withdrawal of subjects
- Treatment of subjects
- Assessment of efficacy and safety

Elements of the clinical trial protocol

- Statistics
- Direct access to source data
- Quality control and assurance
- Ethical considerations
- Data handling and record keeping
- Financing and insurance
- Publication policy
- Supplements

Ethics Committee & Competent Authority

- The Ethics Committee approves the clinical trial protocol (Directive 2001/20/EC of the European Parliament and of the council)
- The Competent Authority evaluates the aspects related to quality of the IMP and to the preclinical data
- Differences between EU Member States exist in the exact responsibilities in this context of the Ethics Committee and the Competent Authority

Ethics Committee & Competent Authority

- Preclinical data are important in the early phases and a number of protocol elements are largely determined by the preclinical data
- Therefore the EC/CA evaluating the preclinical data, will also take into account the way these data are reflected in the protocol

Exploratory clinical trials

- Exploratory clinical trial:
- With limited preclinical testing
- With limited clinical dose
- Not aiming at the MTD
- Answer questions in humans to decide on further development
- A choice between candidates is often made

Exploratory clinical trials

- Most elements of the protocol are similar to a classical phase I trial
- In addition the rationale for the exploratory approach should be given
- The dose limitation should be justified
- The effect to be obtained should be justified
- Not in severely ill patients and not with very toxic products

Safety aspects

- Guideline EMEA/CHMP/SWP/28367/07 on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
- Potential need for staggered dosing should be addressed in the protocol:

– Mechanism of action (novelty, target)

– Shape and slope of dose response curves

– Species differences (mechanism, PK)

- Based on literature and on non-clinical data obtained with the product

Safety aspects

- Predicted (adverse) effects should be monitorable and this should be addressed in the protocol:
  - Biomarkers and signs preceeding unacceptable effects should be proposed and justified
  - Degree of effect that is acceptable with regard to safety should be defined
  - Degree of effect that is desired to study PD should be defined

Safety aspects

- Clear stopping rules should be defined with regard to allowed maximal pharmacodynamic or adverse effect and exposure (Cmax and/or AUC based)
- Based on predictions from animals and use of biomarkers and signs of activity
- Based on animal exposures at effective doses and NOAEL
- General monitoring to detect unpredicted effects (physical examination, ECG, vital signals, biochemistry)

Safety aspects

- Treatment strategy for adverse effects should be described in case of a predictable risk of a certain type of adverse reaction in humans:
- Specific antidotes when available
- Clear plan of availability of supportive treatment emergency facilities and medical staff
- Length and nature of monitoring should be described

Starting dose

- The starting dose should be justified in the protocol
- Based on NOAEL in the most sensitive species
- Conversion of animal doses to human doses should be justified
- Predictions of human exposure in comparison to active doses in animals (AUC, Cmax)
- Safety factor should be justified and not be used to compensate for lack of data but only to cover the uncertainties related to the conversion from animal to human data

Starting dose

- Minimal Anticipated Biological Effect Level should be considered and is mandatory for substances acting on a new target and high risk compounds
- In vitro data on the effect of the sustance on human and animal targets and in vivo data on the plasma concentration and AUC at the dose required to obtain pharmacodynamic effect in animals could be used to establish a safe starting dose

Factors determining safety factor

- Species differences
- Non-sigmoid shape and steep slope of dose response curve
- Large variation in effect or exposure
- Non-linear PK
- Novelty of target, mechanism or structure
- The target cells, organ or system
- Potential to cause pleiotropic effects
- Serious and severe potential effects
- Non-monitorability of effects

Dose escalation

- It should be noticed that a safe starting dose is not a guarantee that no adverse effects will occur with the product, as these may only become observable once a certain level of activity is reached
- Therefore the pharmacodynamic effects and PK data in humans collected at the lower doses may be used in conjunction with the preclinical data to decide upon further dose escalation and pauses at critical points may be build in the protocol to evaluate all data

Dose escalation

- By using human data it may be possible to reduce uncertainties about translation of animal data to humans
- The protocol should indicate how pausing in the dose escalation phase will be used to guide decisions on dose escalation
- The protocol should indicate which factors need to be considered to take decisions on dose escalation

Maximal dose

- A maximal dose or exposure should be indicated and justified
- Based on adverse effects in animals
- Based on exposure in humans at lower doses
- To remain below animal exposure at NOAEL
- No reason to exceed a dose causing 100 % target engagement or a certain level of activity unless to determine safety margin
- Once a sufficient safety margin between expected therapeutic and the maximal dose is established: need to further increase dose?

Dose escalation

- In humans, unexpected findings may be observed.
- If these occur they should also be taken into account in the decision making on dose escalation before they become a SUSAR
- Because they are unpredicted, these unexpected findings cannot be taken into account in the original protocol but they should prompt to reflection and may be included in amendments if necessary

Flexibility

- Early phase clinical trials are exploring the effects of a new potential medicinal product in humans and clinical trial protocols may need to be “open” to accommodate changes as required by the first findings in humans
- Therefore clear decision trees for dose escalation, number of subjects to be included in a certain cohort etc. should be given
- Notification of decisions and feedback on observed effects may be required

Flexibility

- If the decision tree is no longer followed, a substantial amendment should be submitted or a new trial application may even be needed
- Umbrella protocols can be considered to some extent (e.g. SAD and MAD studies in combination with a PD study) if a clear rationale and decision tree is presented
- Umbrella protocols should always be justified and may be considered unacceptable

Flexibility

- Is there always a gain in time with umbrella protocols?
- Approval of new studies can go fast
- Making decisions much in advance may also lead to wrong decisions
- Many assumptions in decision trees, if considered acceptable, may necessitate more controls (DMC, reporting to Ethics Committee and/or Competent Authority)

Study participants

- Healthy volunteers are usually preferred for early phase studies:
- They are in general less prone to variation
- They may be at less risk than patients who may already be more prone to adverse reactions
- Adverse effects may be easier to detect because « background » events are less likely to occur
- No risk for interference from previous treatment

Study participants

- Stable patients with moderate disease may be included
- To decide on further development (exploratory clinical trials)
- PD effect may be better supported than in healthy persons
- Expression of the target occurs only in disease
- PD effect may be different in disease
- Special groups of healthy volunteers like elderly, obese… may be considered

Study participants

- Reproductive toxicity studies are generally not available before early phase studies are started
- Women not of child bearing potential can be included in clinical trials if the repeated dose toxicity studies were conducted including evaluation of female reproductive organs
- Women not of child bearing potential are usually defined as permanently sterilised or 12 months no menses

Study participants

- Women of child bearing potential can only be included
- After reproductive toxicity studies were conducted

OR

- Under certain conditions (ICH M3)
- Pregnancy should be adequately prevented

1) Pregnancy test
2) Highly effective contraception
3) Entry into study after confirmed menses

Study participants

- The primary aim of a phase I study is to study safety and tolerability as well as early pharmacokinetics
- Healthy male volunteers are still preferred and most often recruited for early phase studies and exceptions should be justified

Use of challenge agents

- If challenge agent has a marketing autorisation, the use can be justified easily
- If challenge agent is well known, refer to literature or to existing human data to justify the dose, route of administration, duration of treatment….
- If the challenge agent is new, provide preclinical data in support of its use

Oncology: general considerations

- Products were toxic and clinical trials were conducted in patients with advanced disease and with metastases
- The recently adopted ICH S9 guideline is still aiming at such patients
- The fact that patients are very ill and have a bad prognosis is no reason to neglect normal preclinical testing allowing for proper risk evaluation and management
- A rationale to use new agents should be provided

Oncology :dosing in patients

- Reach a therapeutically active dose as soon as possible
- It should be possible to predict active doses and exposure from preclinical studies
- For some products pharmacological activity may be considered to calculate starting dose from an activity and safety perspective
- The dosing schedule and the number of treatment cycles should be justified based on preclinical studies, the concomittant treatment and the condition of patients

Oncology: dosing in patients

- The highest non-severely toxic dose in animals is often the most important determinant of the clinical starting dose (1/10th of rodent or 1/6th of non-rodent HNSTD)
- It should be possible to predict the nature of adverse effects and predictive signs for upcoming adverse effects should be proposed

Oncology: dosing in patients

- When toxicity is expected and no marker of toxicity is identified, dose escalation should proceed with smaller steps
- Slope of dose response curve may need to be considered to determine dose escalation steps
- Maximal dose is not limited by the preclinical data but is should be considered that it may not be worthwile to increase the dose above 100% target engagement
- A flexible decision tree may have advantages

Oncology: end of treatment

- In particular for early phase trials the end of treatment and end of trial may be difficult to define
- Usually patients can be treated until disease progression or until toxicity makes further use of the IMP impossible
- However, the limited preclinical testing does not allow unlimited exposure and therefore it should be well defined when treatment of the patient will end.

Oncology: combination treatment

- Interaction with other therapies and potential for (cross-) resistance should be considered
- Data to support a rationale for the combination should be provided prior to starting the clinical study
- For a trial in advanced cancer combination toxicology studies with known products may not be required, but for products with novel mode of action this may be needed

Oncology: background treatment

- Background treatment to be specified in the protocol
- Background treatment may be a product used within its marketing autorisation or outside its marketing autorisation but based on clinical practice
- Background treatment may be less well defined: Standard Of Care
- SOC may differ slightly between centres and countries

Oncology: the future?

- Anti-tumour agents become more specific and less toxic:
- Selection of patients may need to be justified based on the mechanism of action
- When human volunteers are involved in early phase clinical trials the same rules apply as for other indications
- As less toxic products are being studied, the approach to study anti-tumour agents may shift to practice for other agents, and particularly if survival is considerable