Setting the stage

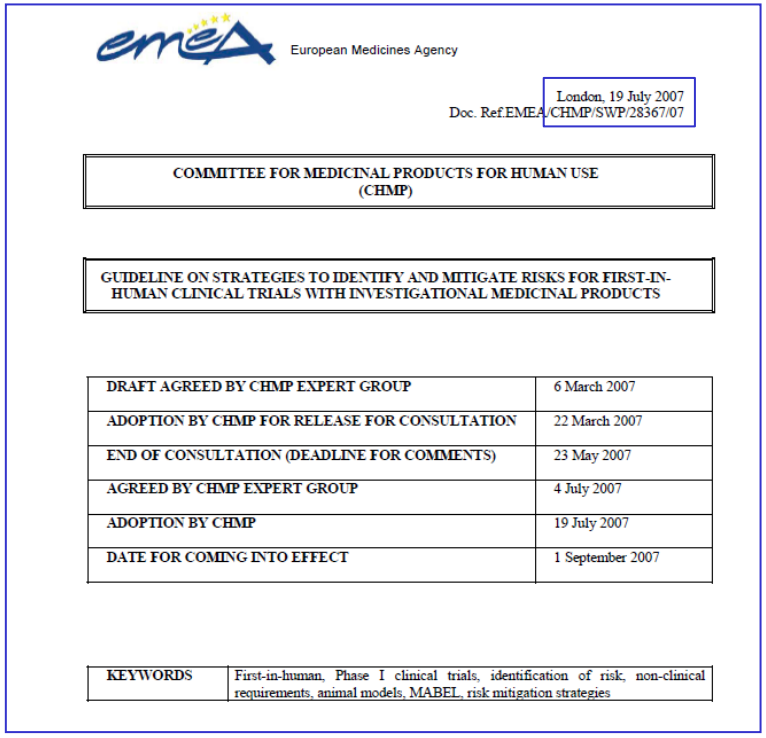
The revised EMA guideline on early phase clinical trials

Dr. med. K. Breithaupt-Grögler, MD
Board Certified Specialist in Clinical Pharmacology
-kbr- clinical pharmacology services
Frankfurt am Main / Germany
breithaupt-groegler@t-online.de

Why a specific guideline for FIH?

- In 2006 (FIH trial TGN-1412, single ascending doses), 6 healthy subjects developed a severe cytokine-release syndrome, all subjects survived, some with persistent injuries
- In 2016 (FIH trial BIA-10-2474, inegrated protocol, multiple ascending dose), 5 healthy subjects developed CNS lesions in MRI scans, one subject died

EMA guideline on FIH / early trials



European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

KEYWORDS	First-in-human, Phase I clinical trials, identification of risk, non-clinical requirements, animal models, MABEL, risk mitigation strategies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

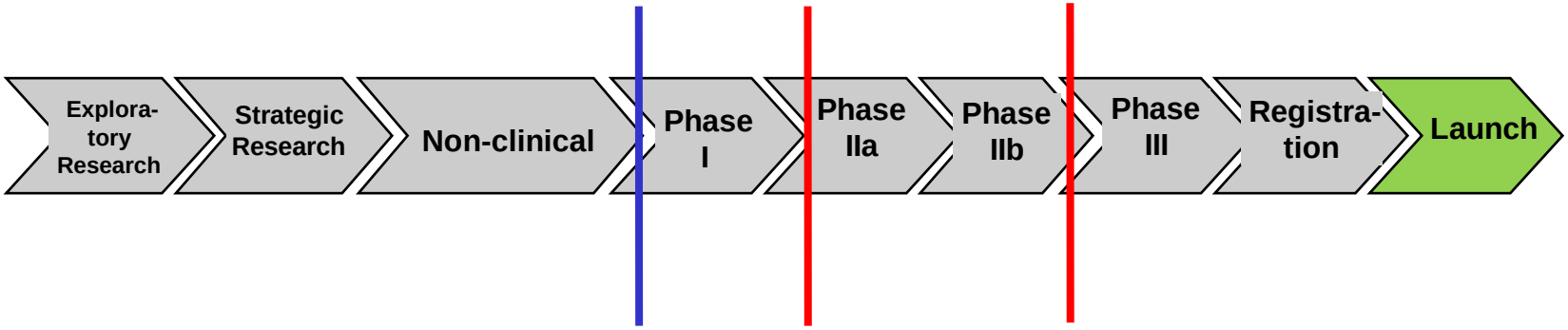
20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

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

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

FIH and early clinical trials ?



- This guideline covers FIH/early clinical trials including those which generate initial knowledge in humans on tolerability, safety, PK and PD.
- These trials may also include collection of data on e.g. food or drug interactions, different age groups or gender, proof of concept and relative bioavailability of different formulations.
- These trials are often undertaken in healthy volunteers but can also include patients.
- The guideline applies to all new chemical and biological investigational medicinal products.

Early phase integrated protocol

… the increasing practice is to perform FIH and early phase clinical trials with integrated protocols that combine a number of different study parts …

- Single ascending doses
- Multiple ascending doses
- Food effect
- Pharmacodynamic effects
- ECG (safety) assessments
- Gender comparisons

Guideline based on general considerations

- Early clinical development has intrinsic element of uncertainty in relation to possible benefits and risks of a novel drug candidate
- Uncertainty may arise from mode of action, presence or absence of biomarkers, nature of target, relevance of animal models and/or findings in non-clinical safety as well as characteristics of the trial population (healthy volunteers or patients, genetic and phenotypic polymorphisms influencing PD and PK)
- Process of designing development programme is governed by the attempt to reduce this uncertainty step-by-step
- Sponsors and investigators should identify, a priori for each clinical study, the potential risks that might arise and apply appropriate risk mitigation strategies
- Sponsor's responsibility to define the degree of uncertainty of the IMP and to provide a description of how the risk(s) will be handled within the design and conduct of the FIH/early clinical trial

Risk mitigation strategies

Based on the degree of uncertainty:

- Ensure adequate quality of the IMP
- Conduct additional non-clinical testing, to obtain data of relevance for the risk assessment which may include data to support assessment of relevance of animal models
- Apply a scientific rationale in the selection of the starting dose, for dose escalation and when defining the maximum exposure to be achieved
- Apply appropriate risk mitigating measures in the design and conduct of FIH/early clinical trials

In defining an appropriate development programme for an IMP, information on safety needs to be integrated from many sources and reviewed in an iterative process.

FIH / Early Phase Guideline - Content

- Executive summary
- Introduction (background)
- Scope
- Legal basis
- General considerations
- Quality aspects
- Non-clinical aspects
- Dosing selection for FIH and early clinical trials
- Planning and conduct of FIH and early clinical trials

FIH / Early Phase Guideline - Content

6. Non-clinical aspects

6.1. Demonstration of relevance of the animal model

6.2. Nature of the target

6.3. Pharmacodynamics

6.4. Pharmaco- and toxicokinetics

6.5. Safety pharmacology

6.6. Toxicology

FIH / Early Phase Guideline - Content

7. Dosing selection for FIH and early clinical trials

7.1. General aspects

7.2. Starting dose for healthy volunteers

7.3. Starting dose for patients

7.4. Dose escalation

7.5. Maximum exposure and dose

7.6. Moving from single to multiple

7.7. Route of administration

7. Dosing selection

7.1. General aspects

- ✓ Careful dosing selection of an IMP is a vital element to safeguard the subjects
- ✓ Special attention should be given to the estimation of the exposure anticipated to be reached at the initial dose to be used in humans and to subsequent dose escalations to a predefined maximum expected exposure
- ✓ All available non-clinical information and clinical data emerging during the trial should be taken into consideration
- ✓ **Starting dose and a maximum exposure, as well as dose escalation steps** should be **justified and outlined in the protocol**. **Decision-making criteria** for adapting the planned dose escalation steps based on emerging clinical data should also be **described in detail**. Deviations from the pre-specified dose escalation and decision-making criteria would warrant the submission of (a) substantial amendment(s)
- ✓ **Provide rationale for what is planned**

7. Dosing selection

7.2. Starting dose for healthy volunteers

- ✓ NOAEL (no observed adverse effect level) can serve as the starting point for determining a reasonably safe starting dose. Exposures achieved at the NOAEL in the most relevant animal species should be used for estimation of an equivalent exposure for humans
- ✓ Exposure showing PD effects in the non-clinical pharmacology studies should also be determined and these data should be used to determine the minimal anticipated biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans

7. Dosing selection

7.2. Starting dose for healthy volunteers

- ✓ The starting dose for healthy volunteers should be a dose expected to result in an exposure lower than the PAD
- ✓ Depending on the level of uncertainty, starting dose should either be related to MABEL, PAD or NOAEL
- ✓ Apply a safety factor taking into account:
  - Novelty of active substance
  - Pharmacodynamic characteristics, including irreversible or long lasting findings and the shape of the dose-response curve
  - Relevance of animal models used for safety testing
  - Characteristics of the safety findings
  - Uncertainties related to estimation of the MABEL, PAD and the expected exposure in humans
  - Monitorability of target organ effects?

7. Dosing selection

7.3. Starting dose for patients

- ✓ Similar considerations apply
- ✓ The goal of selecting the starting dose for patients, i.e. where there are no previous data in healthy volunteers, is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use
- ✓ In some instances, a starting dose substantially lower than the human expected pharmacological dose may not be appropriate

7. Dosing selection

7.4. Dose escalation

- ✓ State the maximum fold increase in dose/exposure from one cohort to the next, as well as a maximum number of cohorts to be evaluated
- ✓ Choice of dose levels should include an estimate of exposure levels to be achieved
- ✓ Dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the non-clinical studies and adapted following review of emerging clinical data from previous cohorts
- ✓ Take into account the steepness of the dose/exposure-toxicity or dose/exposure-effect curves and uncertainties in the estimation of these relationships
- ✓ How reliable can potential adverse effects be monitored in humans?
- ✓ Consider smaller dose increments in case of non-linear PK, particularly in the later parts of SAD/MAD, if clinical data reveal substantial differences from non-clinical data, or saturation of target / plateauing of exposure
- ✓ Changes in dose levels may require a substantial amendment

7. Dosing selection

7.5. Maximum exposure and dose

- ✓ Pre-define an expected maximum exposure level in the protocol for each study part
- ✓ Without approval of a substantial amendment this should not be exceeded
- ✓ Maximum exposure should be justified based on all available non-clinical and clinical data, including PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range
- ✓ In general, the maximum exposure of healthy volunteers should be within the estimated human pharmacodynamic dose range
- ✓ Exceeding exposure levels may be carefully explored in healthy volunteers if scientifically justified and considered acceptable from a safety perspective, however a maximum tolerated dose (MTD) approach is considered inappropriate
- ✓ In patients, the MTD should be clearly defined and not be exceeded once it has been determined

7. Dosing selection

7.6. Moving from single to multiple dosing

- ✓ Dosing interval and duration of dosing for all multiple dosing cohorts / study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and all data from subjects in previous single dose cohorts
- ✓ Pay particular attention to linear versus non-linear PK, the PK half-life versus duration of action, and the potential for accumulation
- ✓ State maximum duration of dosing in the protocol for every cohort
- ✓ The expected exposure after multiple dosing (C_{max} and $AUC_{0\text{-}tau}$) should have been covered during preceding single ascending dose parts/trials.

7. Dosing selection

7.7. Route of administration

- ✓ Based on the non-clinical data, the characteristics of the IMP, and the intended therapeutic use
- ✓ A slow infusion may be more appropriate than a bolus injection to allow for a timely discontinuation of the infusion to mitigate an adverse outcome

FIH / Early Phase Guideline - Content

8. Planning and conduct of FIH and early clinical trials

8.1. General aspects
8.2. Protocol
8.2.1. Overall design
8.2.2. Integrated protocols
8.2.3. Choice of subjects
8.2.4. Subject assessments and interventions
8.2.5. General considerations for all cohorts
8.2.6. Precautions to apply between treating subjects within a cohort
8.2.7. Precautions to apply between cohorts and study parts
8.2.8. Data review for decision
8.2.9. Stopping rules
8.2.10. Monitoring and communication of adverse events/reactions
8.3. Documentation of sponsor and investigators responsibilities
8.4. Investigator site facilities and personnel

8. Planning / conduct of FIH and early trials

8.1. General aspects

- Trials should be designed in a way that optimises the knowledge to be gained from the study without exposing excessive numbers of subjects while ensuring the safety of participants
- Safety should not be compromised in the interests of speed of acquiring data or for logistical reasons
- Risk mitigation activities should be proportionate to the degree of uncertainty and the potential risks identified

8. Planning / conduct of FIH and early trials

- ✓ Key aspects of the design to be addressed in trial protocol:
  - Choice of study population
  - First/starting dose, maximum dose and exposure and maximal duration of treatment
  - Route and rate/frequency of administrations; inclusion of a placebo
  - Recommendation to include a PD measure
  - Half-life (PK/PD) of the IMP if the same subjects are participating in multiple cohorts (washout times, accumulation for multiple dosing parts)
  - Number of subjects per cohort
  - Sequence and interval between dosing of subjects within the same cohort
  - Dose escalation increments, transition to next dose increment cohort or next study part
  - Stopping rules
  - Safety (and/or effect) parameters to monitor; intensity of monitoring
  - Trial sites

8. Planning / conduct of FIH and early trials

8.2.2 Integrated protocols

- Pre-define all parts and criteria to move from one part to another as well as possible modifications in integrated protocol
- When definite doses cannot be predefined in all study parts, dose selection criteria should be established in the protocol, integrating data from previous study parts
- Consider feasibility to review and adapt planned study design based on emerging clinical data; changes outside pre-defined criteria need a substantial amendment.
- Overlap of SAD and MAD parts may be acceptable, provided scientifically justified and supported by decision points. Review of available data required before starting MAD part
- Other single dose parts (e.g. food interaction) could be conducted in parallel to the SAD part provided dose and exposure equal to or lower than preceding SAD cohort (all relevant data reviewed, no stopping criteria met)

8. Planning / conduct of FIH and early trials

8.2.5 General considerations for all cohorts

- Flexibility can be allowed for number of cohorts, clearly pre-define optional additional cohorts and provide underlying rationale
- Not acceptable to repeat a dose level that met dose escalation stopping rules. If repetition of cohorts is allowed in the protocol, only lower or intermediate dose level acceptable
- Inclusion of the same subjects across multiple cohorts, for example as part of an alternate cohort dosing scheme, is possible if scientifically justified
- Re-enrolment into higher dose cohorts is only possible after an appropriately defined washout period and provided the subject has not met any discontinuation criteria

8. Planning / conduct of FIH and early trials

8.2.6 Precautions to apply between treating subjects within a cohort

- Design administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP (often known as sentinel dosing)
- Allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort
- Apply for all single and multiple dosing cohorts to reduce the risks associated with exposing all subjects in a cohort simultaneously
- Appropriate at later stages of study: steep part of the dose response curve, approaching target saturation levels or maximum exposure levels, non-linear PK, emerging clinical signs or adverse events
- Adequate period of time between first subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse events

8. Planning / conduct of FIH and early trials

8.2.7 Precautions to apply between cohorts and study parts

- Administration to the next cohort should not occur before participants in the immediately preceding cohort have been treated and PK, PD and clinical safety data as appropriate from those participants are reviewed in accordance with the protocol
- Review of all previous cohorts' data in a cumulative manner should also be taken into account
- The planned dose(s) should be adapted accordingly, unanticipated responses may require a revised dose escalation
- Timing between cohorts should be stated in the protocol
- Prior to any further part following (or overlapping with) the SAD part or any other part, sufficient information should be available from completed preceding parts / cohorts

8. Planning / conduct of FIH and early trials

8.2.9 Stopping rules

The protocol should define unambiguous stopping rules which result in an immediate stop to dosing.

Stopping rules should be defined for:

- ✓ final stop to dosing and termination of the trial
- ✓ stopping for an individual subject, at any time in the trial
- ✓ stopping within a cohort during multiple dosing when subjects in a cohort are dosed staggered progression to the next part of the trial
- ✓ any dose escalation parts of the trial

8. Planning / conduct of FIH and early trials

8.2.9 Stopping rules

Stopping rules for healthy volunteer trials should include:

- ✓ a 'serious' adverse reaction (i.e. a serious adverse event considered at least possibly related to the IMP) in 1 subject
- ✓ 'severe' non-serious adverse reactions (i.e. severe non-serious adverse events considered at least possibly related to the IMP) in 2 subjects in the same cohort, independent of within or not within the same system-organ-class

Dose stopping criterion

- ✓ maximum exposure observed in individual subjects within a cohort

8. Planning / conduct of FIH and early trials

8.2.10 Monitoring and communication of adverse events/reactions

- The trial design should provide a specific plan for monitoring for adverse events or adverse reactions
- All clinical staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions
- Of high importance in the protocol is a plan for prompt communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor, all study sites and investigators and trial subjects
- In the case of emerging safety issues (severe or serious adverse reactions), the Sponsor should inform investigators and participants as soon as possible, and at least prior to any planned next dosing

8. Planning / conduct of FIH and early trials

8.3 Documentation of sponsor and investigators responsibilities

- The responsibilities of the sponsor and investigator(s) (as well as any other experts or study staff) in decision making should be clearly defined in the protocol
- The composition of any decision making group or safety review committee should be documented in the protocol. Consideration should be given to the inclusion of independent experts who are (at least) external to the study

8.4 Investigator site facilities and personnel

- FIH/early clinical trials should take place in appropriate clinical facilities and be conducted by trained investigators and medical staff with appropriate levels of training and experience of early phase trials
- FIH/early clinical trials should take place under controlled conditions (e.g. inpatient care)

EMA guideline on FIH and early trials

To sum up

- Intensive and specific planning is required, especially regarding adaptive elements
- All trial aspects, procedures, decision points need to be pre-defined in the protocol ‘in case of …’
- Provide detailed scientific justifications and rationales for what is planned