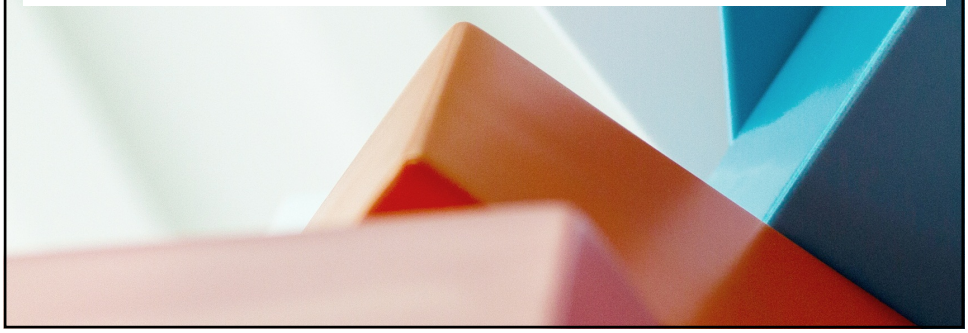
Federal Institute
for Drugs
and Medical Devices

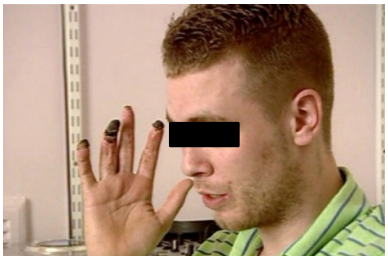
# A regulatory update on the EU guideline on First-in-Human clinical trials

Thomas Sudhop, BfArM, Bonn



## Contents

# Severe incidents in FIH trials 2006 and 2016



http://www.dailymail.co.uk/news/article-1015349/Elephant-Man-drug-trial-victim-set-win-2m-payout-horrific-injuries.html

**2006: TGN-1412 incident (SAD)**
6 HVs survived a severe "cytokine release syndrome", some with permanent damages

http://www.irishtimes.com/news/world/europe/rennes-drug-trial-leaves-one-person-brain-dead-1.2498741

**2016: BIA-10-2474 incident (MAD)**
1 HV died, 4/5 HVs were injured (CNS lesions in MRI scans)

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# Status


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## Focus of the update

- Limitations of the 2007 version
  - Less precise wording
  - Primary focus on non-clinical aspects
  - Phase I aspects only on single ascending dose (SAD) studies
- 2016/2017 version
  - Integrated trial protocols with
    - MAD, SAD, FI, DDI ...
    - Inclusion of healthy subjects and patients
  - Lessons learnt from the BIAL 10-2474 trial
- Guideline intended for new chemical and biological IMPs (no ATMPs)



## General considerations
## Mode of action

- Special attention on
  - Novelty and uncertainty of the mode of action
  - Nature and intensity of effects (e.g. duration, (ir)reversibility)
  - Type and steepness of dose-response relationship (e.g. S-, U-, bell-shaped)
  - Target -> signalling pathways (e.g. multiple pathways), secondary pharmacology, off-target effects
  - Targets addressing biological cascades (e.g. blood coagulation, immune system)
  - Mode of action involves long or irreversible binding to target
    - E.g. effect half life not linked to PK

# General considerations

- Nature of the target(s)
  - Structure, tissue distribution (incl. immune system)
  - Biological effects and down-stream-effects
  - Expression/function in HV and patients
  - Limited data should be high-lighted
- Relevance of animal species models
  - Consider use knock-out/in animals



# Quality aspects

- Determination of strength and potency
- Qualification of the material used
  - Material used in non-clinical studies should be representative of the material to be used for FIH CTs
- Reliability of very small doses
  - Demonstrate that the intended formulation of the doses is suitable
  - Discuss potential risks of reduced accuracy due to
    - Dilution,
    - preparation of very small doses/concentrations, or
    - absorption to the wall of the container or infusion system
  - Discuss compatibility of the product with primary packaging materials and administration systems

## Non-clinical aspects

- GLP Status
  - Sponsor should confirm GLP compliance for all **pivotal** non-clinical safety studies
  - All other studies (e.g. PK and PD) should be of high quality and consistent with the principles of GLP
- Link to 3Rs principles on animal use (Directive 2010/63/EU)



## Non-clinical aspects
## Demonstration of relevance of the animal model

- The search for a relevant animal model should be documented and the model selected should be justified in the IB

- Demonstration of relevance may include comparison with humans of
  - target expression, distribution and primary structure
  - pharmacodynamics
  - pharmacokinetics (metabolism)
  - tissue cross-reactivity studies using human and animal tissues for certain products (e.g. monoclonal antibodies).

## Non-clinical aspects
## Pharmacodynamics

- Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets
- Selectivity and specificity of the IMP and secondary PD should be critically evaluated and documented
- A dose/concentration-response curve of PD effect(s) with sufficient titration steps should be provided
- A state-of-the-art PK/PD modelling approach is recommended
  - Consider repeated dose applications as to be expected in the clinical situation



## Non-clinical aspects
## Pharmacodynamics and toxicokinetics

- PK and TK data should be available in all species used for safety studies
  - should support the interpretation of data from in vivo PD models
- Brief summary of the analytical assays for non-clinical PK and TK analysis should be provided
  - including their accuracy, precision and LOQ
- Exposures at pharmacodynamically active doses in the relevant animal models should be determined and considered especially when PD effects are suspected to contribute to potential safety concerns

## Non-clinical aspects
## Toxicology

- In case of serious toxicity a more cautious approach for human dose setting is expected
- If mortalities or serious toxicity occurred in non-clinical studies, evaluation of putative mechanism is required
  - histopathological examinations
    - necessary in pivotal studies
    - to be considered for dose range finding studies



## Dosing selection for FIH and early clinical trials
## Starting dose

- Based on exposure at NOAEL level in most relevant and sensitive species
- Dose estimation based on state-of-the-art modelling (PK/PD, PBPK) and/or allometric factors
- Determination of MABEL, PAD and anticipated therapeutic dose range (ATD) in humans
  - Target binding / receptor occupancy
- Justified safety factor(s) should be applied
  - Novelty and uncertainty should be taken into account
- In HVs: Starting dose should result in an exposure that is below that which would be expected to produce a PD response

## Dosing selection for FIH and early clinical trials
## Dose escalation

- Dose increases should always be justified and outlined in the protocol
- Dose increment should be guided by dose/exposure-toxicity or dose/exposure-effect relationship defined in non-clinical studies and by emerging clinical data
- The steeper the increase in the dose/toxicity or dose/effect curves the lower the dose increment should be selected
- If evidence/suspect for non-linear PK smaller dose increments especially in later SAD/MAD parts should be considered
- If emerging human data reveal significant differences from the non-clinical, modelling or simulation data, dose adjustment in the protocol is required (subst. amendment)



## Dosing selection for FIH and early clinical trials
## Maximum dose and dose range

- A justified maximum dose or exposure should be pre-defined in the protocol
  - should not be exceeded substantial amendment
- In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers (unless scientifically justified)
- Maximum tolerated dose (MTD)
  - HV: A trial design using a MTD approach is considered to be unethical for HVs
  - Patients: In patients MTD should be clearly defined and not be exceeded

## Planning and conduct of FIH and early clinical trials
## Overall protocol design

- The protocol should describe the strategy for managing risk, including
  - a specific plan to monitor for and manage likely AEs or ARs
  - procedures and responsibilities for modifying or stopping
- In integrated protocols there should be a decision at a predefined time point on proceeding to the next part
- Graphical overall scheme of the trial showing intervals to allow rolling review, timing of all reviews and decision points, is encouraged
- Justified details on the size of the cohorts (active/placebo) should be provided



## Planning and conduct of FIH and early clinical trials
## Integrated protocols

- "Within an integrated protocol all parts need to be predefined, including possible modifications, with specification on the basis of existing data and information, e.g. all non-clinical and, if available, clinical data."
- "Any changes outside the predefined criteria should be communicated to the competent authority(ies) and ethics committee(s), as applicable."
- A certain overlap of SAD and MAD parts may be considered acceptable, if scientifically justified and supported by a decision-tree
  - review of the available data before deciding on starting the MAD part
- Parallel single dose parts parallel to SAD part are acceptable
  - if doses/exposures do not exceed those used in previous SAD cohorts
- Other study parts that involving multiple dosing should not overlap with any earlier SAD or MAD cohorts

# Planning and conduct of FIH and early clinical trials
# Choice of subjects

- Many factors should be considered when deciding on the inclusion of HVs or patients, e.g.
  - any long lasting or irreversible pharmacological effect
  - any immediate and potential long term toxicity
  - the relative presence of the target in healthy subjects or in patients; e.g. cancer patients
  - the possible higher variability in patients
  - the use of other medications with the possibility for adverse reactions and/or difficulties in the interpretation of results
  - the patients' ability to benefit from other products or interventions



# Planning and conduct of FIH and early clinical trials
# Healthy subjects

- Concomitant exposure of subjects to IMPs across trials
  - E.g. national initiatives to prevent over-volunteering of HVs
- **"The key inclusion and exclusion criteria for trials involving HVs should also be in line with <u>normal ranges</u> of vital signs (including ECG) and safety laboratory values"**
  - Discussion process in Germany

Eur J Clin Pharmacol (2017) 73:409–416
DOI 10.1007/s00228-016-2189-8

REVIEW

**Who is a 'healthy subject'?—consensus results on pivotal eligibility criteria for clinical trials**

Kerstin Breithaupt-Groegler[1] · Christoph Coch[2] · Martin Coenen[2] · Frank Donath[3] · Katharina Erb-Zohar[4] · Klaus Francke[5] · Karin Goehler[6] · Mario Iovino[7] · Klaus Peter Kammerer[7] · Gerd Mikus[8] · Jens Rengelshausen[9] · Hildegard Sourgens[10] · Reinhard Schinzel[11] · Thomas Sudhop[12] · Georg Wensing[13]

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5350217/pdf/228_2016_Article_2189.pdf

## Planning and conduct of FIH and early clinical trials Precautions within a cohort

- Sentinel approach
  - Start with 1 + 1 subjects ( 1 active + 1 placebo) simultaneously and review safety data prior dosing other subjects of the same cohort
  - Suitable time period to detect late onset adverse events based on non-clinical and clinical data
  - At the end of the observation period there should be a clearly defined review of all data before dosing of further subjects in the cohort
- Sentinel approach may also be appropriate at later stages, e.g.
  - on the steep part of the dose response curve
  - when approaching target saturation levels
  - when approaching exposure margins to non-clinical NOAELs
  - in case of non-linear PK …



## Planning and conduct of FIH and early clinical trials Precautions between cohorts

- Next cohort may not be dosed unless all subjects of the previous cohort have been treated and safety data and PK data (where available) were reviewed
  - All relevant data of cohort “n” must be reviewed prior starting cohort “n+1”
- The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information
- Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and should be stated in the protocol
- Flexibility to allow for a defined longer review time in the event of emerging data could be accepted
  - Shortening of the review time for any dose escalation always requires a substantial amendment

# Planning and conduct of FIH and early clinical trials
# Precautions between study parts

- In general same approach as between cohorts
- Review of all previous finished study parts and cohorts data in a cumulative manner (PK, PD, safety)
  - Actual data need to be compared to the initial simulated expectations and refined in line with available clinical information.
  - Planned doses should be adapted accordingly, if needed

- "For studies with multiple parts, consideration may be given to submitting an **interim report** to the competent authorities for review **as a substantial amendment** prior to the start of further dosing phases."



# Planning and conduct of FIH and early clinical trials
# Stopping rules

- The protocol should define **unambiguous** stopping rules which result in an immediate stop to dosing
  - Specifiy in the rule if it implies a final end of dosing or a
  - possible temporary halt with dosing re-starting after a full evaluation of available data **and the approval of a substantial amendment**

- Stopping rules should be defined for each of the following:
  - Final stop to dosing and termination of the trial
  - Stopping for an individual subject, at any time in the trial
  - Stopping within a cohort
    - when allowing remaining subjects in a cohort to be dosed after the preceding subjects have completed the first dosing period
    - during multiple dosing
  - Progression to the next part of the trial
  - Any dose escalation parts of the trial

## Planning and conduct of FIH and early clinical trials
## Stopping rules for healthy volunteers

- **Reaching clinical exposure** (Cmax or AUC) equivalent or higher to the exposure achieved at the NOAEL in the most sensitive species
  - adjusted by safety factors if appropriate
- 1 **serious** adverse reaction (SAR) in **one healthy subject**
  - SAR: SAE at least possibly related to IMP
    - Consider SAE as SAR as long as it could not be explained by other factors (subject was considered healthy at the beginning of dosing)
- **Severe** non-serious adverse reactions (AR) in **two healthy subjects** in the same cohort
  - AR: AE at least possibly related to the IMP



## Planning and conduct of FIH and early clinical trials
## Investigator site facilities and personnel

- Appropriate clinical facility
- Conducted by trained investigators
  - with necessary expertise and experience in conducting early phase trials and
  - medical staff with appropriate level of training and previous experience of early phase trials
  - training should include relevant medical expertise and GCP training
- Investigators/medical staff should understand specific characteristics of the IMP
  - e.g. target(s) and mode of action

## Planning and conduct of FIH and early clinical trials Investigator site facilities and personnel

- FIH/early CTs should take place under controlled conditions (e.g. hospitalisation), with the possibility of close supervision of study subjects during and after dosing as required by the protocol
- Units should have immediate access to equipment and appropriately qualified staff for **resuscitating** and stabilising individuals in an acute emergency and **ready availability of intensive care unit facilities**
- Procedures should be established between the clinical research unit and its nearby intensive care unit regarding the responsibilities and undertakings of each in the transfer and care of patients
- All FIH/early CTs for an IMP should preferably be conducted at a **single site**
  - When different sites are involved, this should be justified(!)



## What comes next?

- Update adopted by CHMP for release for consultation
  - November 2016
- Start of public consultation
  - November 2016
- End of public consultation
  - 28 February 2017
- CHMP adoption
  - ?

# Thank you very much for your attention!

## Contact

Federal Institute for Drugs and Medical Devices
Division Scientific Services
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Contact person
Thomas Sudhop, MD
thomas.sudhop@bfarm.de
www.bfarm.de
Tel. +49 (0)228 99 307-4360
Fax +49 (0)228 99 307-3424

Federal Institute for Drugs and Medical Devices