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Revision of the ‚first in human' guideline

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Content

1. Scope and concepts
2. Non clinical aspects
3. Dose Selection
4. Clinical design and conduct

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

Scope:

ALL first-in-human → **EARLY** phase clinical trials

- Integrated protocols

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*EMEA/CHMP/SWP/28367/07 Rev. 1

Concepts

- Concept of: 100%??? → 0% ? *never reached !*
  - **Uncertainty**
    - Knowledge : *‚what is known and what not'*
    - Degree of uncertainty in risk and/or benefit impacts on:
      - → Non clinical studies to perform
      - → Translation to human:
        ‚Dose' selection *First* → *Maximum ;* steps
      - → Risk mitigation

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Concepts (II)

- **Exposure**
  - Plan and decide on exposure; - not ‚dose'
  - Need:
    → Exposure in vivo ‚pharmacological model'
    (active ‚dose' level, pharmacodynamics (PD))
    → Pharmacokinetics (PK), Toxicokinetics; species
    → ***Modeling*** *(PK/PD, PBPK)* ***& simulation***
- **Verfication and adaption *throughout* the trial**
  - Integrated assessment
    - Use all available information
    - Take up emerging (clinical) data
  - Adjust if differences in emerging data to simulated data
  - Informed decision

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Non Clinical Aspects

- Understanding - **Characterisation** of
  - **Primary pharmacology** : *The wanted assumed mode of action*
    - Target including downstream, in vitro - in vivo:
      Potency, duration of action, reversibility,
      Single/**multiple** dosing, saturation, exaggerated PD
    - *Exposure at active level* → modeling (PBPK, PK/PD)
  - **Secondary Pharmacology** : on-target/off-target
    - Findings, affinities, *selectivity*
  - **Safety and Toxicology** : Findings - exposure… **NOAEL**
    - Pharmacology ≈ *adverse*
    - Death → cause ? mechanism?
    - Serious findings – mechanism, reversible, monitorable?

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Non Clinical Aspects - Translation

→ **Relevance** of species, of model

→ Comparison to human : Target, ‚pharmacodynamics', PK

→ Differences ?!

→ Information from human material

• **Translation** to human :

→ Pharmacology – ‚goal in human':

- Mininum anticipated biological effect level (**MABEL**) in humans
- Pharmacologically active dose (**PAD**)
- Anticipated therapeutic range (**ATD**) in humans

→ Pharmacokinetics: Estimated exposure in human

→ Safety/Toxicology: NOAEL … biomarker, safety factor (exposure)

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Dose selection

All parts of clinical trial:

→ Exposure (dose) at **start**

→ **Maximum** exposure (dose)

→ Use all non clinical information

- Level of uncertainty
- Knowledge
- *Relevance and difference*
- Monitoring, safety factor ?!
- Risk mitigation
- Patients: disease

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Dose selection – Maximum Dose

- Maximum exposure and dose
  - Not to be exceeded !
  - Healthy: **within** estimated pharmacodynamic dose range
  - Patients: MTD only if applicable, clearly defined

  - *Exposure > ATD ?*
    - Careful if safe + sci. justify
    - Impact of uncertainty
      - PD-Tox-PK knowledge
  - *Exposure > NOAEL ?*
    - Toxicology studies
    - Relevance of species/finding
    - No tox finding – higher uncertainty
    - ….

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Dose selection

- Dose escalation
  - Maximum fold increase
  - Relationship exposure/PD or /Tox:
    Linearity, steepness … saturation,
    Variability

- Single dose → multiple dose
  - Dosing interval and duration
  - Accumulation: PD, PK and/or Tox

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Dose selection

- Modeling & Simulation →
  Verification of estimates (PD-PK-safety):
  Emerging clinical data fit simulation/expectation?
  - → Adaptions needed
  - → PK analysis online vs. skip or collect dose steps?

- Risk mitigation : Sentinel dosing - yes/no?
  - Uncertainty
  - Steepnes, saturation….

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Clinical – Risk Mitigation

- Risk mitigation
  ≈ uncertainty and potential risks defined
  - Design:
    - Population : healthy -patient
    - Dose/exposure, dose escalation
    - Sequence and interval between dosing - Sentinel dosing
    - Moving within or to next cohort, dose or part : timinig, review
    - Stopping rules
    - Monitoring, routine set and project specific

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Clinical

- **Clear responsibility** define ‚who-what-when'
- Continous ‚integrated' assessment and informed decision
  - Predefined (minimum) data set, quality check and criteria
  - \+ Use all information including emerging (clinical) data
  - E.g. - **Safety – must**
    - **Pharmacokinetics – should**
    - Pharmacodynamics – highly recommended

    → Adaptations if needed as of criteria
- **Rapid communication**
  - Adverse events/ reactions
  - Emerging data
  - Adaptations
  - Especially if multiple sites

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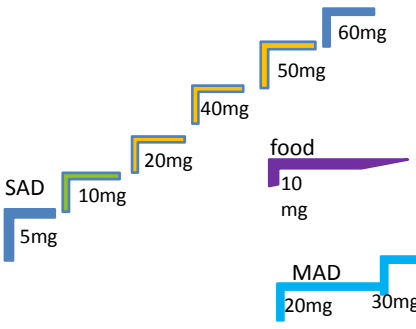
Clinical – Single or Integrated Protocols?



- Planned with non clinical data
- Rules, e.g.
  - Limited overlap
  - Reviews timing/criteria
  - If predefined criteria not met
    →substantial amendment

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Clinical – Stopping Rules

- Clear Stopping rules → immediate stop of dosing
  - → temporary or final
  - → for: study, individual,
    within cohort, dose escalation or/and next part
- Healthy: 1 serious adverse reaction
  2 severe non-serious adverse reaction (in 2 subjects)
  criteria for moderate recommended
- Maximum clinical exposure: Individual rather than mean values

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Overall,

- Widen scope for all early CTs
- General principles like uncertainty, exposure,
  risk mitigation and informed decision
- Use of all data, perform ‚continous' verification and adaptation
- Knowledge of pharmacology (prim.+sec.), mechanism of findings
- Healthy participants stopping rules,
  in-/exlusion criteria within normal range

➢ **Nothing really new**
➢ …however pointed out in more detail

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Thank you very much for your attention!

Questions ?

Contact

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