

Risk mitigation in first in Human protocol

Where do we stand, what can we do different?

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Guidelines



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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

DRAFT

**GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR
POTENTIAL HIGH-RISK MEDICINAL PRODUCTS**



Following the guidelines is an easy way, but there may not be only one way to reach the objective of a safe and informative First in Human Trial

Inclusion/exclusion criteria

- Healthy subjects or patients?
 - Shall we revisit what drives the decision : safety risk & feasibility of the trial, relevance of the population to measure a pharmacological effect
- Are the criteria to be more stringent : beyond « healthyness », shall we consider also former exposure to a number of agents, psychological consideration, familial history of disease?

Protocol guidance

- Staggered subjects in one cohort
 - In a single ascending dose 2+2+4 dosing
 - In a multiple ascending dose 4+4, but quickly overlapping subject treatment
- Data review after each cohort & Decision making
 - Who seats in this review
 - What are the data : Safety, PK (of the current dose, of the previous dose) And pharmacodynamics.
 - Use of modelling approaches to guide the dose escalation
- Stopping rules
 - Finding the right balance : they should be clinically sound
- Allowing to repeat a dose, decrease the dose
 - For a better informed decision

Safety measures

- Are more lab or imaging or clinical examinations the solution?
- What do we really need to implement to best assess tolerability ?
- CNS drug specific questions, still unanswered
 - Usefulness of EEG?
 - Need for brain imaging?
 - Lack of biomarkers of target engagement

Other considerations

- Dose escalation shall be driven by safety but also Pharmacodynamics and PK
 - Biomarkers of target pharmacology may not have been identified
 - PK : PK of the active compound(s), whether they are parent metabolite, (active metabolite , active metabolite & others?)
- Place of a microdose in a first in human plan
 - Usefull for human metabolite identification & PK profile understanding

In the end, we all have the same goal
Safety first to ultimately find a cure.

