

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Göttingen, 28. February 2018

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Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Common considerations:

1. Risk assessment of substance class

or Risk assessment of substance

e.g. mode of action, pharmacology and toxicology (therapeutic window) by sponsors and investigators

- To identify the potential risk factors and

- To appropriate mitigate risks in early (FIH) clinical trials

2. PK-associated thoughts (linearity, non-linearity, steepness of concentration-effect-curve, correlation between PK/PD, optimal exposure, maximum tolerated dose)

3. PD-associated thoughts (POC, optimal effectiveness, duration of effect)

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/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

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Aim of FIH Study:

1. Primary:

- To assess safety and tolerability of new investigational medicinal product

2. Secondary:

- To assess first PK data
- To obtain first PD data (whenever possible, e.g. in patients)

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Methodology of FIH Study:

1. Definition of starting dose
2. Definition of dose escalating steps
3. Definition of stopping rules
4. Definition of maximum tolerated dose
5. Definition of the dose limiting toxicity
6. Definition of AE of special interest

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Methodology of FIH Study:

1. Definition of starting dose

three concepts:

- MABEL – Minimum Anticipated Biological Effect Level

The dose or exposure required at the bottom end of the dose response curve in man

- NOEL – No Observed Effect Level

The highest dose level at which and below which no effects of the test compound are observed amongst the evaluated parameters

- NOAEL – No Observed Adverse Effect Level

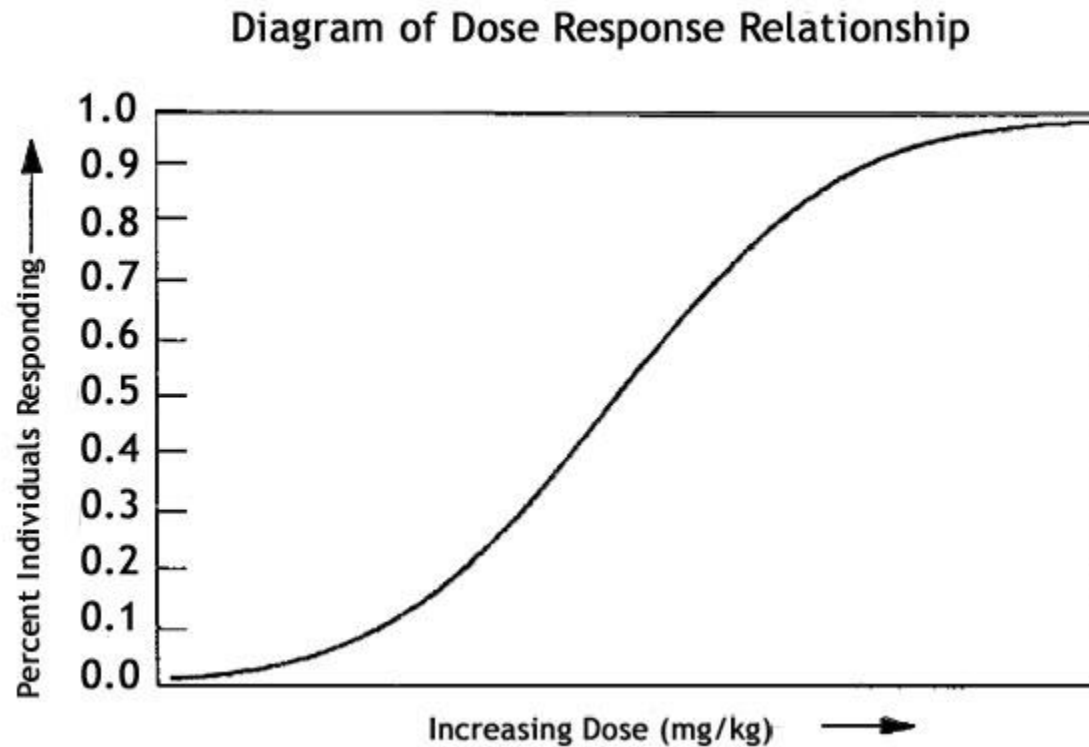
Takes only into account effects which are regarded as adverse

For extrapolation of the safe dose level in man the NO(A)EL is divided by a safety (uncertainty) factor

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Methodology of FIH Study:

1. Definition of starting dose



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Methodology of FIH Study:

2. Definition of dose escalating steps

- 3 + 3 method

Rule-based design(s) assign(s) patients to dose levels according to prespecified rules based on actual observations of target events (e.g. dose-limiting toxicity)

- Continual Reassessment Method (CRM)

Model-based design as alternative to rule-based designs and using Bayesian models or maximum likelihood estimation

The guiding principle for dose escalation in FIM patient studies is to avoid unnecessary exposure of patients to subtherapeutic doses of an agent and to avoid overshooting of the maximum tolerated dose (MTD)

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Methodology of FIH Study:

2. Definition of dose escalating steps

These methods were developed for cytotoxic drugs assuming that both efficacy and toxicity increase with dose.

Consequently, these methods have used **toxicity as the primary endpoint**.

For molecularly targeted agents the dose-efficacy and dose-toxicity curves may differ, and efficacy may occur at doses that do not induce clinically significant toxicity.

For such agents the occurrence of **drug-related biological effects** has been suggested as an **alternate primary endpoint** besides toxicity.

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Methodology of FIH Study:

2. Definition of dose escalating steps

- 3 + 3 method

Cohorts of three patients

1st cohort: treated at a (considered) safe starting dose

Subsequent cohorts are treated at increasing dose levels, fixed in advance

(Dose increments 100%, 67%, 50%, 40%, 30-35% of the preceding dose – modified Fibonacci sequence)

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Methodology of FIH Study:

2. Definition of dose escalating steps

- Accelerated titration designs:

Combine features from variations of the traditional 3 + 3 design and model-based design (for cytotoxic agents)

- Only one patient is included per dose level
- Possibility of intra-patient dose escalation (reduce the number of patients who are treated at subtherapeutic doses)
- The standard 3 + 3 design is used after stopping the accelerated titration phase due to DLT event

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Methodology of FIH Study:

2. Definition of dose escalating steps

- Pharmacologically guided dose escalation

Assumes that dose-limiting toxicities can be predicted by plasma drug concentrations and that animal models can accurately reflect this relationship in humans

Stage 1: Prespecified plasma exposure defined by AUC is extrapolated from preclinical data. PK data obtained for each patient (one per dose level, 100% dose increments) as long as the prespecified plasma exposure is not reached.

When target AUC is reached or if dose-limiting toxicities occur, dose escalation switches to 3 + 3 design with smaller (40%) dose increments.

- *Limited to drugs with small inter-subject PK variability!*

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Methodology of FIH Study:

2. Definition of dose escalating steps

- Continual Reassessment Method and Modifications

Patients treated at the dose thought to be closest to the MTD.

The trial be stopped when six patients assigned to the same dose.

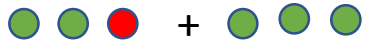
De-escalation and re-escalation of doses are allowed.

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Methodology of FIH Study:

3. Definition of stopping rules

- 3 + 3 method



Stop!



Stop!

The study will be stopped immediately after occurrence of second dose-limiting toxicity event.

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Methodology of FIH Study:

3. Definition of stopping rules

- Alternative rules besides 3 + 3:

2 + 4 (**stopping rule** the same as for 3 + 3)



Stop!



Stop!

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Methodology of FIH Study:

3 Definition of stopping rules

- Alternative rules besides 3 + 3:

3 + 3 + 3 (**stopping rule**: three out of nine experience LDT)



Stop!



Stop!



Stop!



Stop!

Dose escalation and stopping rules in single and multiple ascending dose parts of a FIH trial

Methodology of FIH Study:

3. Definition of stopping rules

- Alternative rules besides 3 + 3:

3 + 1 + 1 (best of five) **stopping rule**: three dose-limiting toxicities are observed



Stop!



Stop!



Stop!

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4. Definition of Maximum Tolerated Dose:

The highest dose of a drug or treatment that does not cause unacceptable side effects.

Will be defined preclinical.

The term “unacceptable” is relative and depends e.g. on the indication for which the drug will be used: vomiting may be acceptable as side effect for cancer treatment, but unacceptable for treatment of other diseases.

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4. Definition of Dose limiting toxicity:

Must be defined in the study protocol and should characterise the kind of AE and the severity

Based on:

- Expert's opinion
- Common databases (e.g. CTCAE – Common Terminology Criteria for Adverse Events), classifying and grading Aes
- Any related SAE

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5. Definition of AE of special interest:

“An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. (Based on CIOMS VI)”

FDA guidance for industry: [E2F Development Safety Update Report](#)

Definition given in the study protocol

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Multiple dose escalation:

Aim:

PK/(PD) characterisation, estimating linearity/nonlinearity and dose proportionality based on results of Single Ascending Dose study.

Cohort size: at least 6 patients per dose

Dose levels and dosing frequency are chosen to achieve therapeutic drug levels within the systemic circulation that are **maintained at steady state for several days** to allow appropriate safety parameters to be monitored. It is usual **for 2 - 3 dose levels** to be studied, at and above the expected therapeutic dose level(s) to determine the 'safety margin' for repeat dose administration.

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Multiple dose escalation:

Stopping rules are the same as for SAD – studies

Definition of doses of MAD should be made based on exposition data obtained in the SAD part of FIH (Optimum).

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Thank you for your attention!