Exploratory clinical trials workshop

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Topics

- Introduction – Definitions
- Nonclinical safety studies to support Early Phase I
- Starting dose and maximum doses
- Different approaches
- Chemistry, Manufacturing and Controls
- Early Phase I clinical trial – Practical aspects
- Conclusion
- References

Introduction – Definitions

- Exploratory clinical trials are those intended to be conducted early in Phase 1
- They are first in man clinical trials with investigational medicinal product
- They involve limited human exposure, have no therapeutic or diagnostic intent, and are not intended to examine maximum tolerated dose

Introduction – Definitions

- They can be used to investigate a variety of parameters such as pharmacokinetics, pharmacodynamics and other biomarkers, which could include receptor binding and displacement
- The aim could be to prove a concept or to select a compound for a full development from different candidates

Exploratory IND Studies FDA January 2006

- Although exploratory IND studies may be used during development of products intended for any indication, it is particularly important for manufacturers to consider this approach when developing products to treat serious diseases
- Exploratory IND studies include drug and biological products

Exploratory clinical trials workshop

Non clinical safety studies to support early Phase I

Starting dose and maximum dose in early Phase I

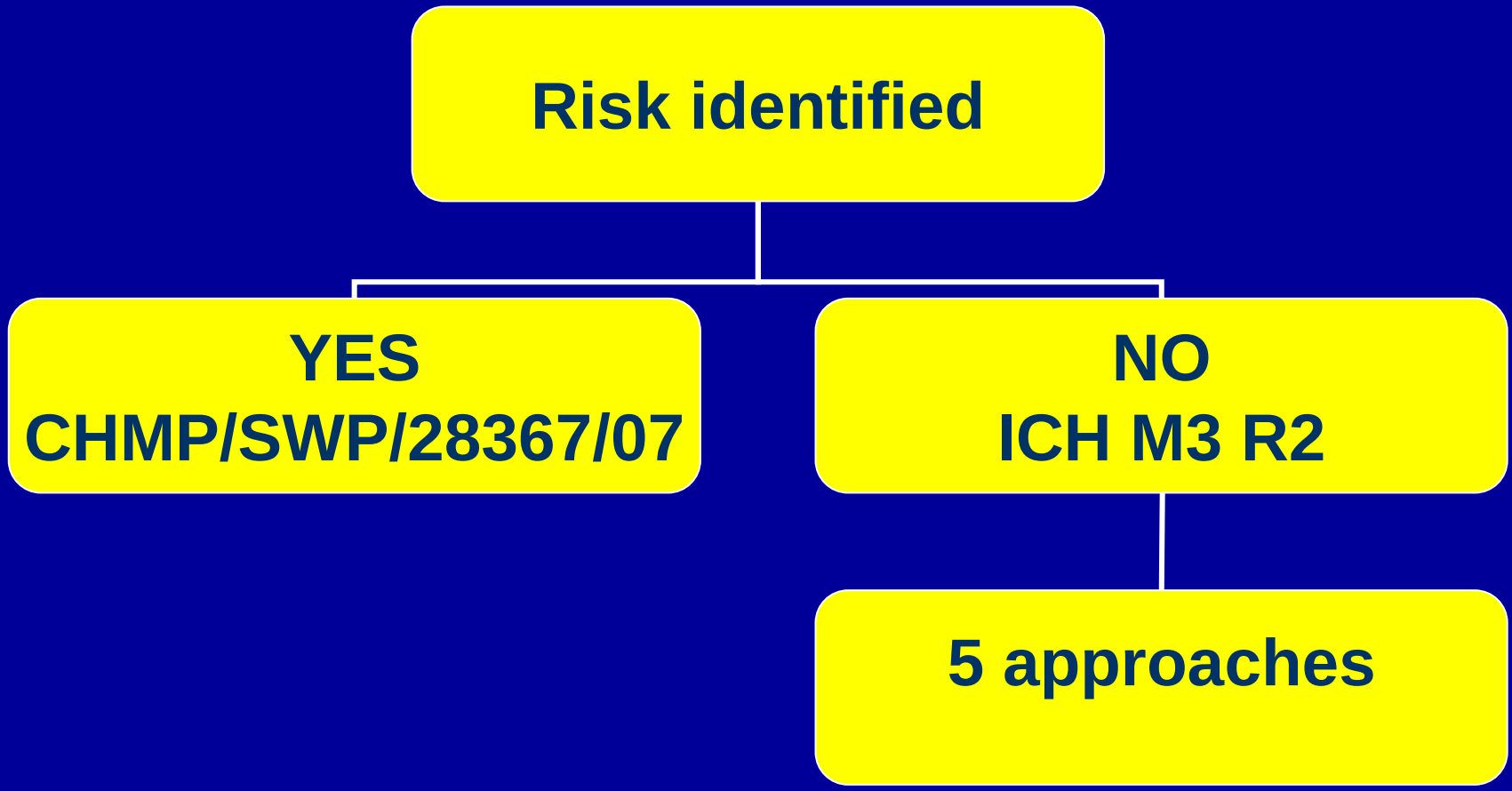
Different approaches

Guideline - Guidance

- **Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products**
  EMEA/CHMP/SWP/28367/07 19 July 2007

- **Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals**
  ICH M 3 (R2) 28 July 2008 CPMP/ICH/286/95

Exploratory Phase I



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

- When planning a first-in-human clinical trial, sponsors and investigators should identify the factors of risk
- Concerns may be derived from particular knowledge or lack of knowledge regarding
  - (1) the mode of action
  - (2) the nature of the target,
  - (3) the relevance of animal models

Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals ICH M3 R2

- **Exploratory clinical studies**

  The amount of nonclinical supporting data that is appropriate in these situations will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing

Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals ICH M3 R2

- **Exploratory clinical studies**

  Five different exploratory clinical approaches are described as examples. However, other approaches not described in this guidance can also be used

  Appropriate starting dose and maximum dose for each approach are included

Approach 1

Dose to be administered	General Toxicity Studies
Total dose ≤ 100 µg; maximum of 5 administrations (no inter dose interval limitations) AND Total dose ≤ 1/100 NOAEL and ≤1/100 pharmacologically active dose (scaled on mg/kg for i.v. and mg/m^2 for oral)	Extended single dose toxicity study in one species, usually rodent, by intended route of administration with TK or via the i.v. route. A limit dose of 10 mg/kg in rats (~6000 times the 100 µg clinical dose on a mg/kg comparison basis) can be used

Close to microdose position paper

Approach 1

Dose to be administered	Start and max dose
Total dose ≤ 100 µg; maximum of 5 administrations (no inter dose interval limitations) AND Total dose ≤ 1/100 NOAEL and ≤1/100 pharmacologically active dose (scaled on mg/kg for i.v. and mg/m^2 for oral)	Maximal and starting doses can be the same but not exceed 100 µg

Close to microdose position paper

Approach 2

Dose to be administered	General Toxicity Studies
Total cumulative dose ≤ 500 μg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted $t_{1/2}$) AND each dose ≤ 100 μg AND each dose < 1/100 of the NOAEL and <1/100 of the pharmacologically active dose	7 day toxicology study in one species, usually rodent, by i.v. route or intended route of administration, with TK, haematology, clinical chemistry, necropsy data and histopathology. A limit dose of 10 mg/kg in rats (~6000 times the 100 μg clinical dose) can be used.

New

Approach 2

Dose to be administered	Start and max dose
Total cumulative dose ≤ 500 μg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted $t_{1/2}$) AND each dose ≤ 100 μg AND each dose < 1/100 of the NOAEL and <1/100 of the pharmacologically active dose	Maximal daily and starting doses can be the same, but not exceed 100 μg

New

Approach 3

Dose to be administered	General Toxicity Studies
Single sub-therapeutic or intended therapeutic dose	Extended single dose toxicity studies in both the rodent and non-rodent by intended clinical route of administration with TK, haematology, clinical chemistry, necropsy data and histopathology. For this situation the top dose should be MTD, MFD or limit dose

Previously proposed by FDA (1996), not accepted in ICH M3

Approach 3

Dose to be administered	Start and max dose
Single sub-therapeutic or intended therapeutic dose	Starting dose should be based on the types of toxicity findings observed in the most sensitive species and a consideration of the pharmacologically active dose. Regional guidance concerning starting dose selection, as available, should be consulted.

Previously proposed by FDA (1996), not accepted in ICH M3

Approach 3

Dose to be administered	Start and max dose
Single sub-therapeutic or intended therapeutic dose	Maximum dose can be that yielding up to ½ NOAEL exposure in the most sensitive species, in cases where any relevant toxicity observed in animals is anticipated to be monitorable and reversible in human

Previously proposed by FDA (1996), not accepted in ICH M3

Approach 4

Dose to be administered	General Toxicity Studies
Single or repeated dose (up to 14 days) exploratory studies into the therapeutic range but not intended to evaluate clinical maximum tolerated dose	Standard 2-week repeated dose toxicity studies in rodent and non-rodent where dose selection is based on exposure multiples of anticipated clinical AUC at maximum dose

Previously proposed by EFPIA to SWP

Approach 4

Dose to be administered	Start and max dose
Single or repeated dose (up to 14 days) exploratory studies into the therapeutic range but not intended to evaluate clinical maximum tolerated dose	Starting dose predicted exposures should not exceed 1/50th the NOAEL in the more sensitive species on a mg/m^2 basis. Regional guidance, as available, should be consulted

Previously proposed by EFPIA to SWP

Approach 4

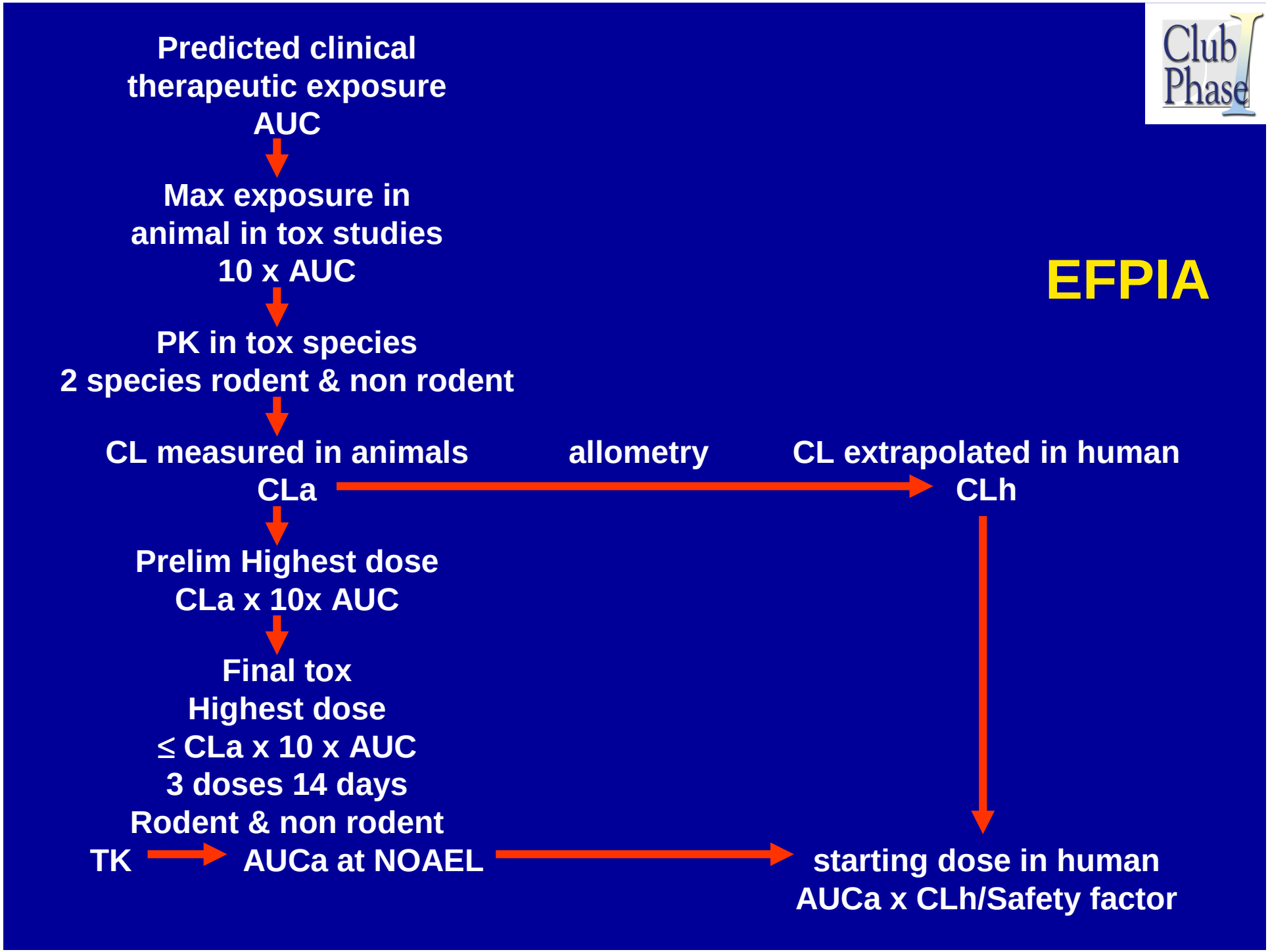
Dose to be administered	Start and max dose
Single or repeated dose (up to 14 days) exploratory studies into the therapeutic range but not intended to evaluate clinical maximum tolerated dose	With toxicity in both species, the maximum clinical dose should be based on standard risk assessment considering the nature, severity, monitorability of the nonclinical findings, but typically would not exceed the lowest NOAEL AUC

Previously proposed by EFPIA to SWP

Approach 4

Dose to be administered	Start and max dose
Single or repeated dose (up to 14 days) exploratory studies into the therapeutic range but not intended to evaluate clinical maximum tolerated dose	Without toxicity in both species, clinical dosing up to 1/10 the lower exposure in either species at the highest dose tested in the animal is recommended. When only one species demonstrates toxicity, the maximum clinical dose would be based on the lower of the above two paradigms

Previously proposed by EFPIA to SWP


Predicted clinical therapeutic exposure AUC
Max exposure in animal in tox studies 10 x AUC
PK in tox species 2 species rodent & non rodent
CL measured in animals CLa
allometry
CL extrapolated in human CLh
Prelim Highest dose CLa x 10x AUC
Final tox Highest dose ≤ CLa x 10 x AUC 3 doses 14 days Rodent & non rodent
TK
AUCa at NOAEL
starting dose in human AUCa x CLh/Safety factor
EFPIA
Club Phase 1

Approach 5

Dose to be administered	General Toxicity Studies
Single or repeated dose up to duration of dosing in non-rodent up to maximum of 14 days; into therapeutic range but not intended to evaluate clinical maximum tolerated dose	Standard 2-week repeated dose toxicity study in rodent (with justification of the rodent as an appropriate species). Confirmatory study in non rodent (n=3) at rodent NOAEL exposure with duration of a minimum of 3 days and at least the intended clinical study duration

Close to FDA exploratory IND

Approach 5

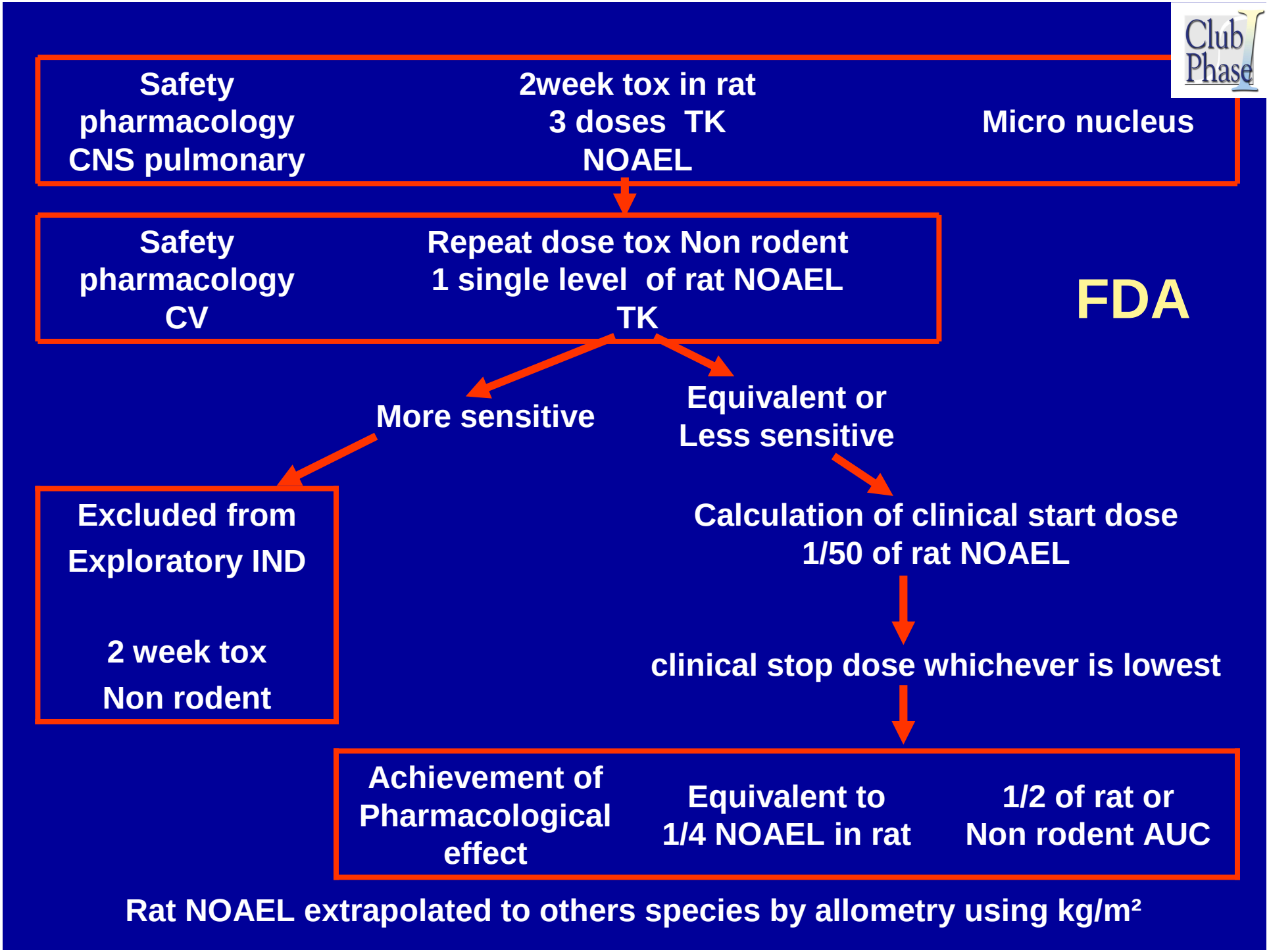
Dose to be administered	Start and max dose
Single or repeated dose up to duration of dosing in non-rodent up to maximum of 14 days; into therapeutic range but not intended to evaluate clinical maximum tolerated dose	Starting dose predicted exposures should not exceed 1/50 the NOAEL In the more sensitive Species on a mg/m2 basis. Regional guidance, as available, should be consulted

Close to FDA exploratory IND

Approach 5

Dose to be administered	Start and max dose
Single or repeated dose up to duration of dosing in non-rodent up to maximum of 14 days; into therapeutic range but not intended to evaluate clinical maximum tolerated dose	The maximum exposure in human should not be Higher than the AUC at NOAEL in the non-rodent species or than ½ the AUC at the NOAEL in the rodent species, which ever is lower

Close to FDA exploratory IND


Club Phase I
Safety pharmacology CNS pulmonary
2week tox in rat 3 doses TK NOAEL
Micro nucleus
Safety pharmacology CV
Repeat dose tox Non rodent 1 single level of rat NOAEL TK
FDA
More sensitive
Equivalent or Less sensitive
Excluded from Exploratory IND
2 week tox Non rodent
Calculation of clinical start dose 1/50 of rat NOAEL
clinical stop dose whichever is lowest
Achievement of Pharmacological effect
Equivalent to 1/4 NOAEL in rat
1/2 of rat or Non rodent AUC
Rat NOAEL extrapolated to others species by allometry using kg/m²

Chemistry, Manufacturing and Controls information

Quality aspects should not be a source of risk for first-in-human

Drug Substance

- Structure
- Characterisation
- Physico-chemical chracteristics
- Impurities

Drug Product

- Composition
- Grade and qualification of excipients
- Sterility

Drug Substance / Drug Product

- Manufacturing process and controls
- Analytical procedures
- Specifications
- Stability
- Packaging
- Certificates of analysis
- GMP

Early Phase I clinical trial

Practical aspects

Early Phase I clinical trial

- The rules to be respected are the same as for any clinical trial
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 requires that clinical trials are submitted for approval by the competent authorities of each Member State where the trial is performed
- The status of early Phase I should be clearly mentioned in the submission and in the protocol

Early Phase I clinical trial

- The safety, rights and well-being of subjects participating in first in human studies is the paramount consideration as they would not normally be expected to derive any therapeutic benefit
- Scientific Advice on Early Phase I clinical trial may be requested from National Competent Authorities or the EMEA

Protocol

- Objectives
- Design
- Study population (volunteer ? patients ? paediatric ?...)
- It could be appropriate that administration will be sequential. An adequate period of observation between the administration of the medicinal product to the first, second and subsequent subjects could be necessary
- Assessments criteria and endpoints should be validated

Protocol (approach 3 to 5)

- Dose escalation scheme
- Information on exposure, effect, and safety from the preceding dose should be taken into account
- The number of subjects per dose increment depends on the variability of both PK and PD parameters and the trial objectives. While larger cohorts are likely to provide more precise data, they may not be necessary to fulfil the objectives of the study

Stopping rules and decision making

- The protocol should define stopping rules during the trial
- The trial should be stopped as soon the objective is reached or when it appears that it will be impossible to reach it
- It should define processes and responsibilities for making decisions about dosing of subjects, dose escalation and stopping the trial

Investigator site facilities and personnel

- First-in-human trials should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early Phase trials and medical staff with appropriate level of training and previous experience of first-in-human studies. They should also understand the investigational medicinal product, its target and mechanism of action

Informed Consent of Trial Subjects

- The investigator should fully inform the subject
- The written informed consent form should be signed and personally dated by the subject

Informed Consent of Trial Subjects

- **Both the informed consent discussion and the written informed consent form should include among others explanations :**
  - **That the trial involves research with no clinical benefit**
  - **Those aspects of the trial that are experimental**
  - **The risks or inconveniences to the subject depending on the chosen approach**

Conclusion

Approach 1	**Single 100µg max** **Repeated 5x20 µg max**	**Microdose** Receptor occupancy biodistribution
Approach 2	**Repeated 5x100 µg max**	
Approach 3	**Single subtherapeutic or intented therapeutic dose**	**Subtherapeutic or therapeutic dose** PK PD PK/PD
Approach 4	**Single/repeated up to 14 days therapeutic dose range**	
Approach 5		

Conclusion

- Exploratory clinical trials are those intended to be conducted early in Phase 1, before dose escalation, tolerance and safety trials
- They can be already submitted in the countries of the European Union (?)
- Request for Expert Scientific Advice from National Competent Authorities or the EMEA is encouraged, mainly for approach 3 to 5

Conclusion

- Exploratory clinical trials involve a limited number of subjects with limited exposure, have no therapeutic or diagnostic intent, and are not intended to examine maximum tolerated dose
- They are not a substitute for the classical Phase I
- Following an Exploratory clinical trial, if one investigational medicinal product is selected for a full development program, a classical Phase I should be done after appropriate non clinical safety studies

References

- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 19 July 2007
- Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals ICH M 3 (R2) 28 July 2008 CPMP/ICH/286/95
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001
- Position paper on non-clinical safety studies to support clinical trials with a single microdose. EMEA/CHMP/SWP/2599/02/Rev1 (23 June 2004)

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- Guidance for Industry, Investigators and Reviewers, Exploratory IND Studies. FDA, January 2006
- Concept paper on the development of a CHMP guideline on the non-clinical requirements to support early phase I clinical trials with pharmaceutical compounds. EMEA/CHMP/SWP/91850/2006 (30 June 2006)
- Guidance to the conduct of exploratory trials in Belgium. Working Document Federal Agency for Medicines and Health Products
- Report of the international expert meeting on Exploratory clinical trial application and microdosing. 15 Sept 2007. BfArM (Germany)

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- Table Ronde dans le cadre des Entretiens de Giens 2008, Thérapie, à paraître.
- First-in-man clinical trials : Estimation of the starting dose, definition of dose progression and protocol of administration to volunteers. AFSSaPS 25/07/2006 reviewed 5/09/2006
- Guidance for Industry :Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA July 2005