

Germany's Regulatory Authorities' approach to approval for First-in-Man trials with new chemical entities (NCEs)

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Lessons needed to be learned from TGN1412

- Sponsors / Pharmaceutical companies
- CROs
- Ethic Committees
- Competent Authorities
- Trial subjects

How to improve current practise?

- First in man trial have multiple risks due to limited data on the IMP and the interaction of IMP and human body
- Unfortunately this part of clinical development has virtually no commonly accepted guidelines
- Therefore, an European guideline document is strictly required
 - Today the first meeting of an European working group takes place in London
 - BfArM has drafted an internal concept paper on NCEs which will be discussed in London

Risk Assessment by Risk Classes

- High Risk Trials
 - Difficult to express general guidance
 - Require a very special assessment
- Non-High Risk Trials
 - Intermediate risk trials
 - Low risk trials

Definition of High Risk Trials

Monoclonal Antibodies (mAb)*

1. The mAb employs a new mechanism of action
2. The mAb addresses a target that lacks appropriate animal models
3. The mAb comprise a new type of engineered structural format

NCEs

1. The NCE is new in class and employs a new mechanism of action. It is reasonable to consider that the mechanism of action might fundamentally affect clinical relevant important vital systems such as the respiratory, immune, cardiovascular, gastrointestinal tract, CNS, and other vital body systems
2. The NCE is new in class and addresses a target or pathway that lacks relevant nonclinical models.

*Schneider CK, Kalinke U, and Löwer J. TGN1412 - a regulator's perspective. Nature Biotechnology 2006;24:493-6

Intermediate / Low Risk Trials

Intermediate Risk Trials

- neither classified as high risk trial nor as low risk trial

Low Risk Trials

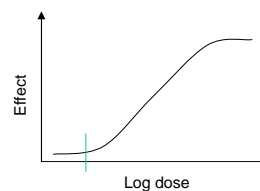
- IMP is member of a well known and well characterised class of medicinal products or is second in class and the class has well described pharmacological properties and
- prior clinical trials did not exert any unforeseeable risk than a clinical trial should be considered as a low risk trial.

Trial Population

- Health status
 - Healthy volunteers or patients
 - Definition of “healthy”
- Gender
 - Women in ‘first in man’ trials?
- Age range
- Ethnicity

Starting Dose

- Characteristics of an optimum and safe starting dose
 - It does not cause any clinically measurable effect
 - neither pharmacodynamic
 - nor toxic effects
 - dose prior MED / PAD (minimal effective dose, pharmacologically active dose)
 - The next higher dose causes first pharmacological effects (if detectable in healthy volunteers) without toxic effects
 - MED

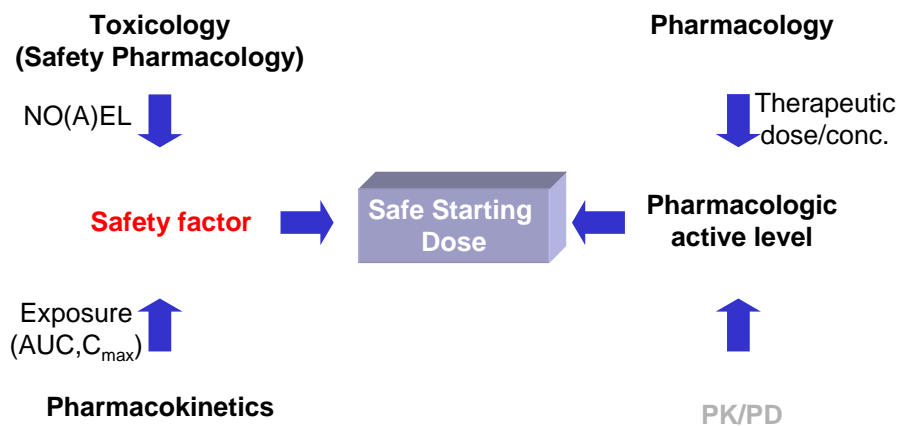


How to obtain a safe starting Dose

- Standard approach: NOAEL / Safety factor (≥ 10)
 - Usually derived from doses rather than exposures
 - NOEL, PAD (Pharmacologically active dose)
 - MABEL (Minimum anticipated biological effect level)
- Allometric Methods according FDA Guidance
 - Human equivalent dose (HED) according FDA recommendations is usually calculated on animal NOAELs
 - PAD adjustment might be necessary

Guidance for industry and reviewers: Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers, July 2005, <http://www.fda.gov/CDER/guidance/5541fnl.pdf>

Safe Starting Dose in Humans



Preclinical Considerations

- Integrated risk assessment from pharmacology and toxicology (safety pharmacology) data
- Pharmacology and toxicology are connected by (systemic) exposure
- Exposure data allow better estimates and extrapolations
 - PK data from most human like species

Dose Regimen

- Number of subjects per dose step (cohort)
- Number of subjects to be dosed at the same time
- Time lag between dosing of the next subjects of
 - the same dose level
 - the next higher dose level
- Dose progression factor
- When to stop

When to stop

- Common approach
 - From MED (minimum effective dose) to MTD (maximum tolerated dose)
 - Nevertheless MTD not needed to be assessed in every IMP
- How to assess the MTD?
 - From MID (Minimum intolerated dose) to MTD
 - MTD => last dose level below MID

Dose Progression

- Standard procedure
 - Arithmetic or geometric increase
- Relevant factors
 - Steepness of the slope of dose/effect and dose/toxicity relations
 - Therapeutic range in nonclinical models
 - Predictability (raw estimate) of the effects of the next dose step
 - Potential pharmacodynamic effects (if any)
 - Potential side effects
 - ...

Cohort Size

- With larger cohorts usually more precise data can be obtained, but larger cohorts put more subjects at risk and increase the costs of clinical development programs
- Common standard is an A + P design
 - with A = 6 to 10 subjects receiving the active product and
 - P = 2 to 4 subjects receiving placebo

Number of subjects dosed simultaneously

- High risk trials
 - not more than one subject
 - sequential administration design
- Intermediate risk trials
 - not more than two subjects per new dose level at first
- Staggered administration designs
 - suitable for different cohort sizes (6+2, 8+3, 10+3 ...)

Staggered Administration Design (6+2)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Dose 1	2A+1P	4A+1P									
Dose 2		2A+1P	4A+1P								
Dose 3			2A+1P	4A+1P							
Dose 4				2A+1P	4A+1P						
Dose 5					2A+1P	4A+1P					
Dose 6						2A+1P	4A+1P				
Dose 7							2A+1P	4A+1P			
Dose 8								2A+1P	4A+1P		
Dose 9									2A+1P	4A+1P	
Dose 10										2A+1P	4A+1P

A: Active medicinal product P: Placebo

Usually 8 subjects per day, with one additional study day

Staggered Administration Design (8+3)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Dose 1	2A+1P	3A+1P	3A+1P									
Dose 2		2A+1P	3A+1P	3A+1P								
Dose 3			2A+1P	3A+1P	3A+1P							
Dose 4				2A+1P	3A+1P	3A+1P						
Dose 5					2A+1P	3A+1P	3A+1P					
Dose 6						2A+1P	3A+1P	3A+1P				
Dose 7							2A+1P	3A+1P	3A+1P			
Dose 8								2A+1P	3A+1P	3A+1P		
Dose 9									2A+1P	3A+1P	3A+1P	
Dose 10										2A+1P	3A+1P	3A+1P

A: Active medicinal product P: Placebo

Time lag between administered Doses

- High risk trials
 - Individually calculated, risk based lag time
- Intermediate risk trials
 - Time lag between the first two subjects of each new dose level should be based on appropriate nonclinical estimates
 - t_{max} -based approach
 - Adjustment might be necessary in case of observed events with late onset
 - For most trials a day by day dose escalation is suitable

“Integrated Protocols”

- Integration of several phase I studies into one trial
 - Interestingly suggested by large CROs (customer retention?)
 - Might lead to safety issues in early phase I
- Single dose escalation (first in man) should not be combined with multiple dose escalation
 - Results from the single dose study usually required to assess the risk of multiple dose study
 - Germany provides a fast track procedure for phase I trials (14 days)