Dose selection based on Minimal Anticipated Biological Effect Level (MABEL) for biologicals and high risk small molecules: case studies & discussion

Bruno Boutouyrie-Dumont, MD
Director, Sr TM Expert, ATI TM,
Novartis Institute for BioMedical Research (NIBR)
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Introduction

First Dose to Man : general principles

- First dose to Man : major step and major milestone in drug development
- Often performed in Healthy Volunteers (except oncology)
- But less and less rarely in Patients with the targeted disease or the “pathway” disease
- Question 1 : Dose(s)/**Exposure(s)** to be assessed ?
- Question 2 : Assessments of safety ?
- Question 3 : Pharmacodynamic assessments ?

Guidance for Industry

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

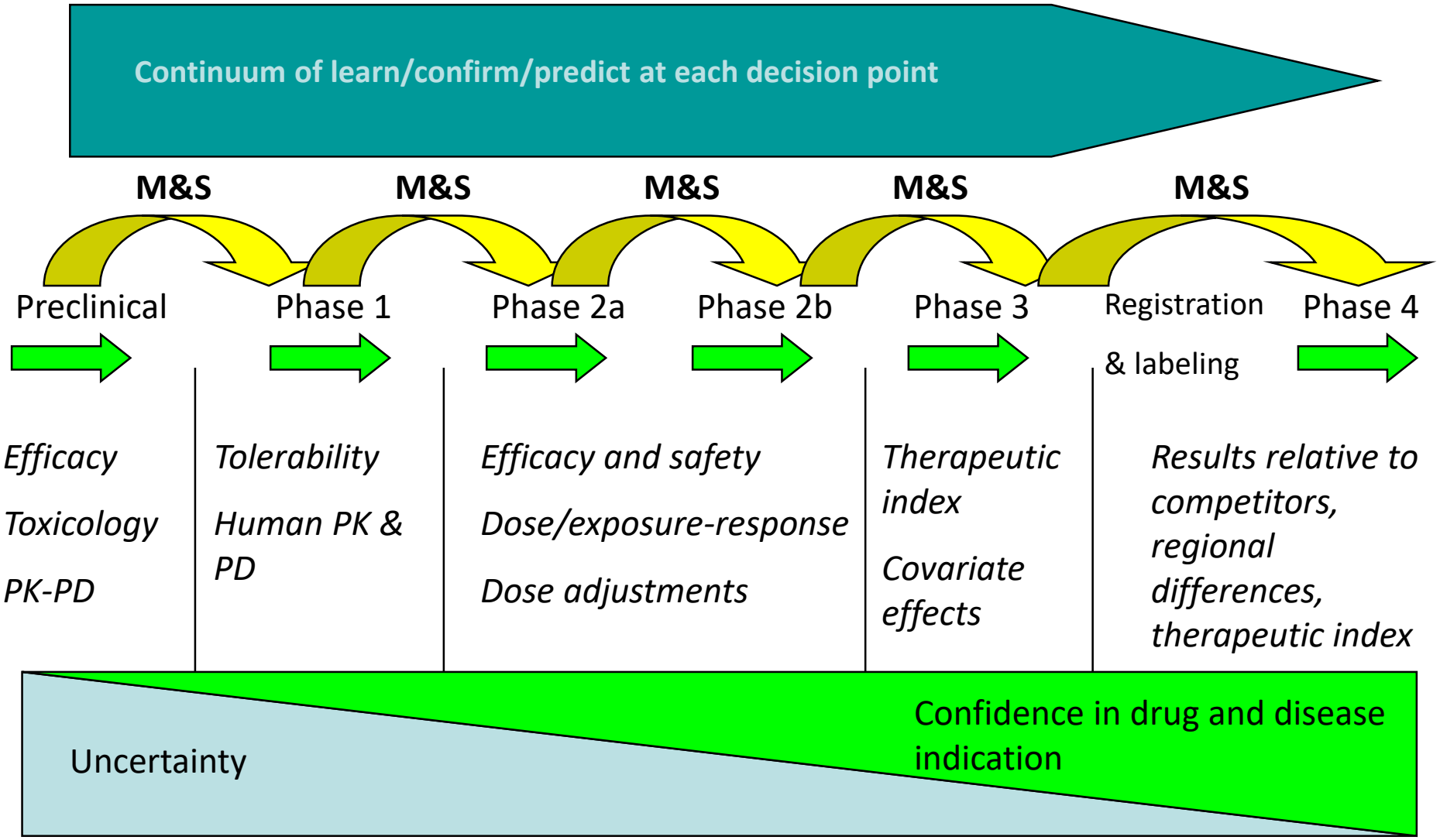
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Drug Evaluation and Research (CBER)

January 2010
ICH

Revision 1

Drug development and model building

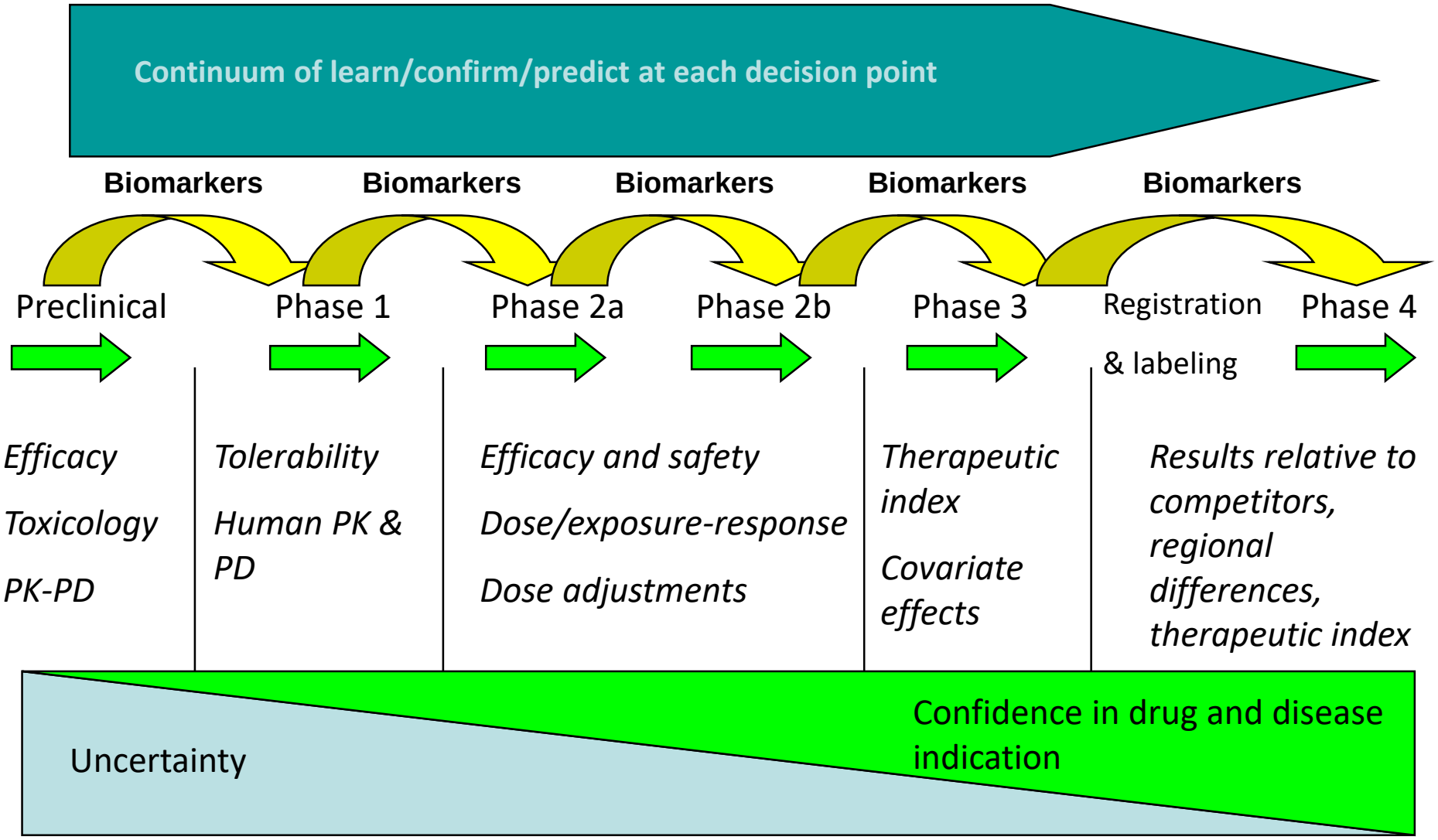
Learning and confirming



R.L. Lalonde et al., Clin.Pharmacol.Ther.;82:21-32 (2007)

Drug development and model building

Learning and confirming



R.L. Lalonde et al., Clin.Pharmacol.Ther.;82:21-32 (2007)

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

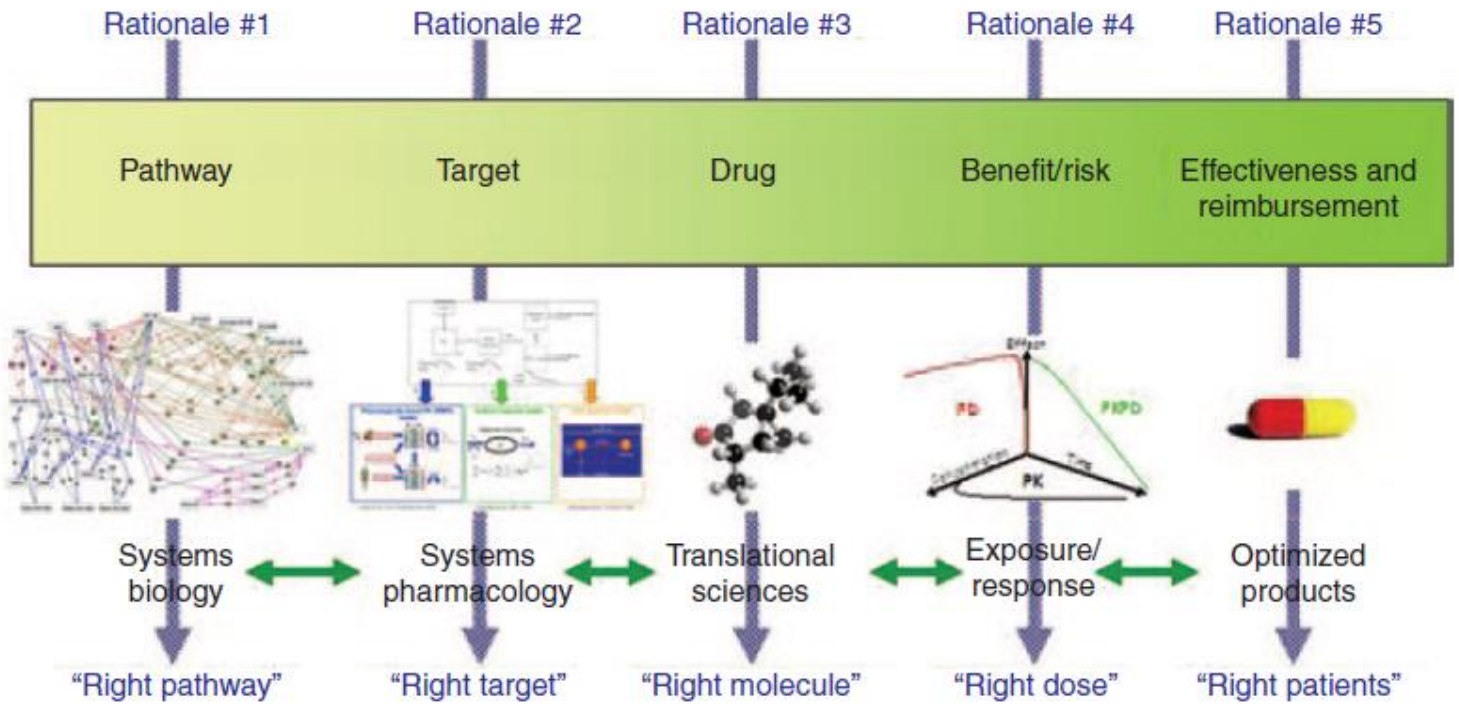


Figure 1 The evolution of model-based drug development (MBDD). Adapted from ref. 2.

PA Milligan, MJ Brown, B Marchant, SW Martin, PH van der Graaf, N Benson, G Nucci, DJ Nichols, RA Boyd, JW Mandema, S Krishnaswami, S Zwillich, D Gruben,RJ Anziano, TC Stock and RL Lalonde

Clinical Pharmacology & Therapeutics,93:6, June 2013, 502-514

1st : Understand/Integrate NC Data (Translational)

M3(R2) D. General Principles (1.4)

- The development of a pharmaceutical is a **stepwise process** involving an evaluation of **both animal and human** efficacy and safety information.
- The goals of the nonclinical safety evaluation generally include a characterization of toxic effects with respect to **target organs**, **dose dependence**, **relationship to exposure**, and, when appropriate, **potential reversibility**.
- This information is used to estimate an **initial safe starting dose** and dose range for the human trials and to **identify parameters for clinical monitoring** for potential adverse effects.
- The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterize potential adverse effects that might occur under the conditions of the clinical trial to be supported.

2nd : Progressive/Sequential/Adaptive Clin Trials

M3(R2) D. General Principles (1.4)

- Human clinical trials are conducted to investigate the efficacy and safety of a pharmaceutical, **starting with a relatively low systemic exposure in a small number of subjects**.
- This is followed by clinical trials in which **exposure** to the pharmaceutical usually **increases by duration** and/or **size of the exposed patient population**.
- Clinical trials should be extended based on the demonstration of adequate safety in the previous clinical trial(s), as well as on additional nonclinical safety information that becomes available as clinical development proceeds.

3rd : Continuous Data Monitoring Process (early D)

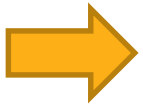
M3(R2) D. General Principles (1.4)

- Serious adverse clinical or nonclinical findings can influence the **continuation of clinical trials**. Within the overall clinical context, these findings should be evaluated to determine the appropriateness and design of additional nonclinical and/or clinical studies.
- Clinical trials are conducted in phases for which different terminology has been utilized in the various regions. This M3(R2) document generally uses the terminology as defined in the ICH E8 guidance (Ref. 2).
- However, as there is a **growing trend to merge phases** of clinical development, in some cases this document also relates the nonclinical studies to the duration and size of clinical trials and the characteristics of the subjects included.

“Right” first dose : Must Be SAFE

Dose(s) to be assessed

- Te Genero accident



- MABEL approach :

European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

MABEL approach

EMA guidance (2007)

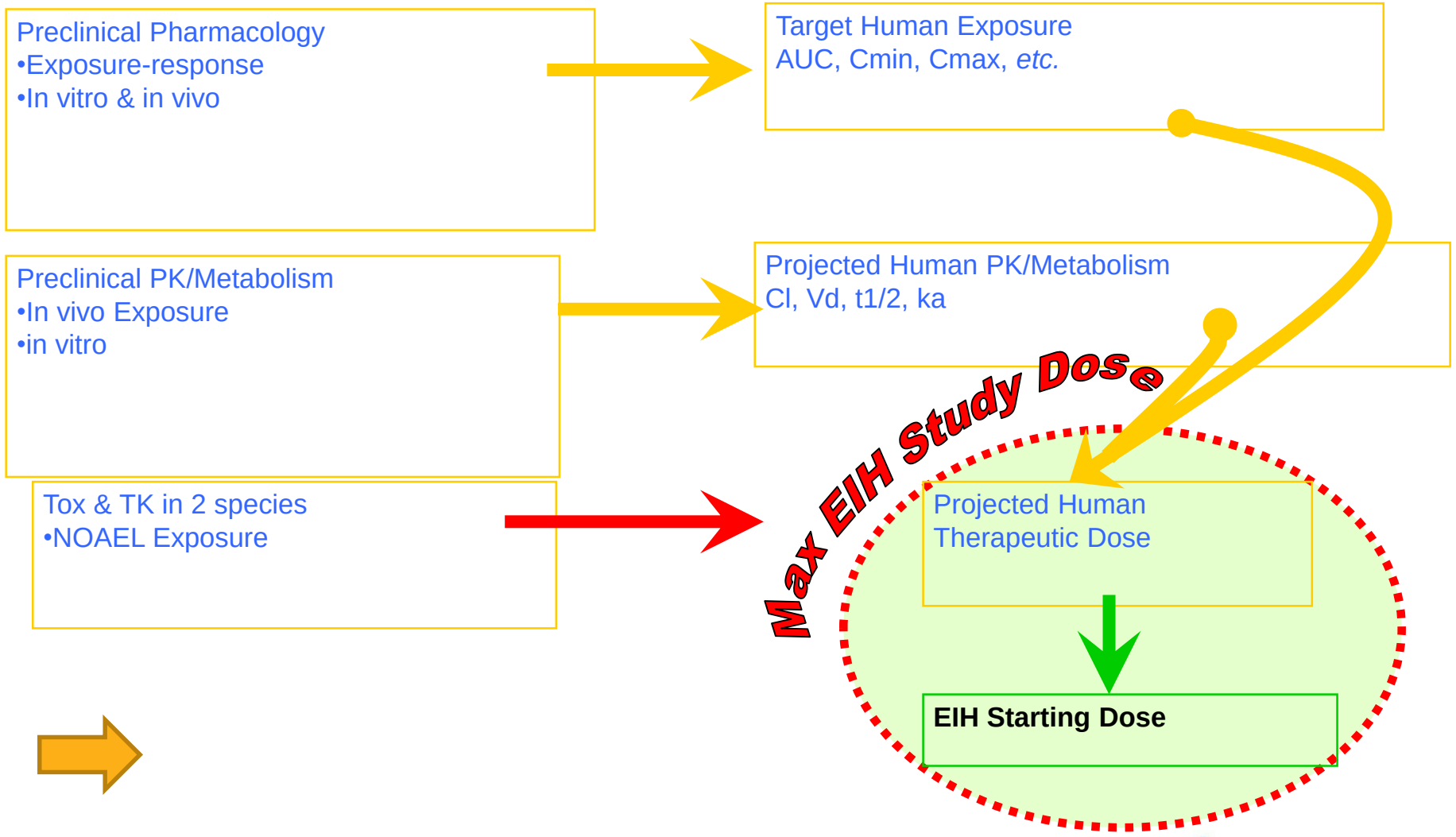
- The ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans.
- The calculation of MABEL should utilise all in vitro and in vivo information available from pharmacokinetic/pharmacodynamic (PK/PD) data such as:
  - i) target binding and receptor occupancy studies in vitro in target cells from human and the relevant animal species;
  - ii) concentration-response curves in vitro in target cells from human and the relevant animal species and dose/exposure-response in vivo in the relevant animal species.
  - iii) exposures at pharmacological doses in the relevant animal species.
- **Wherever possible, the above data should be integrated in a PK/PD modelling approach for the determination of the MABEL.**

Optimal use of PBPK and MBDD

Dose(s) to be assessed

- List all available data :
  - In vitro data : EC50, IC50, concentration-effect curve, ...
  - In vivo data : animal models and corresponding pharmacokinetics
- Estimate **concentrations** (free & total) for :
  - 10 to 25% of maximal effect if an agonist
  - 25 to 50% of maximal effect if an antagonist
- Estimate expected concentrations (Cmax) in Man :
  - At best by PBPK and MBDD methods
  - Or by allometric scaling of animal pharmacokinetics

Exposure-guided EIH : MABEL approach



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Phase 1 trials

- Objectives
  - Assess safety and tolerability
  - Characterize dose-limiting adverse reactions
  - Determine maximum dose associated with acceptable safety profile
  - Characterize pharmacokinetic parameters
  - Explore drug metabolism and drug interactions

Maximum Recommended Starting Dose (MRSD)

- Principles in selecting an MRSD
  - avoid toxicity at the initial clinical dose
  - allow reasonably rapid attainment of the trial objectives (tolerability and PK)
- Algorithmic approach based on administered doses and observed toxicities
- Alternate approaches based on animal pharmacokinetics and modeling

FDA Guidance for Industry : Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers – July 2005

MRSD: Key Concepts

- No Observed Adverse Effect Levels (NOAEL): The highest dose tested in animal species that does not produce a significant increase in adverse effects compared to control group
- Human Equivalent Dose (HED): Conversion factor applied that converts mg/kg dose for each animal species to a mg/kg dose in humans
- Selection of animal species
  - The most sensitive species is chosen (i.e. the species in which the lowest HED can be identified)
  - Some instances, especially with biologics, appropriate animal species used based on in vitro binding and functional studies

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

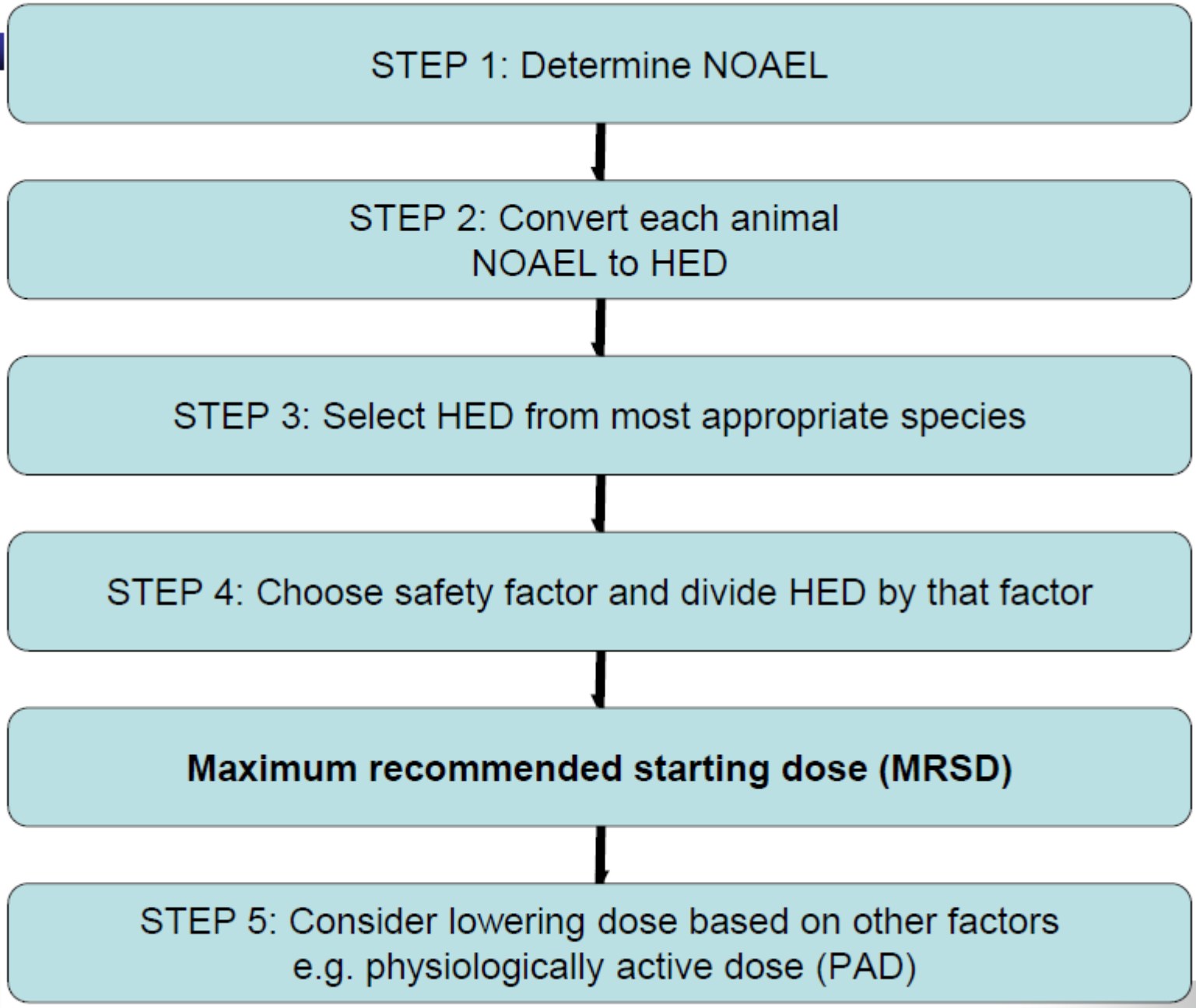
Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

$$HED = \text{animal dose in mg/kg} \times (\text{animal weight in kg}/\text{human weight in kg})^{0.33}.$$

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.


STEP 1: Determine NOAEL
STEP 2: Convert each animal NOAEL to HED
STEP 3: Select HED from most appropriate species
STEP 4: Choose safety factor and divide HED by that factor
Maximum recommended starting dose (MRSD)
STEP 5: Consider lowering dose based on other factors e.g. physiologically active dose (PAD)

Remarks from the French expert committee

Bial accident in January 2016

- The trial in Rennes was conducted in a specialized centre (Biotrial) of sound reputation. An interval was present between the end of a cohort and the start of the next one.
- No neuropsychological assessment with clinical interview and cognitive tests
- Geometric dose escalation ...
- Maximal dose tested : 20 to 50 times higher than therapeutic dose (exposure ?)

Recommendations from the Fr. expert committee

Bial accident in January 2016

1. Need for comprehensive preclinical pharmacology
2. Neuropsychological assessment with clinical interview and cognitive tests needed for CNS compounds
3. Adaptative ajustment of doses based on PK exposure of previous doses
4. Dose administration sequence could be transferred to MAD so as not to expose all subjects from the same cohort at the same time
5. Dose escalation strategy ... Keep common clinical and pharmacological sense.
6. Access to data from ongoing or previous first-in-human and Phase 1 trials ... (European FDA ?)

“Right” dose/exposure escalation

Dose(s) to be assessed

- Bial (BIA 10-2474) accident : to be understood ...
- Sentinel dosing : 1 subject D 1 then 1 subject D 3 then 4 subjects
- In healthy volunteers : not an issue but time for development ?
- In patients : possibly an issue as activity is of interest !
- Typical escalation if «10» is expected therapeutic :
  - Up to ED/EC/IC 50 : 1, 3, 10, 30, 100
  - Up to ED/EC/IC 90 : 1, 2, 4, ...
  - Above : 1, 1.5, 1.33, ...
- Clinical supplies ?
- Formulation to be used ?

Maximal dose/exposure to be assessed ?

Dose(s) to be assessed to characterize "MTD"

Maximal dose (MD) to be assessed should be justified by :

- a clinical development plan (CDP) …
  - Expected therapeutic exposure
- Potential drug drug interaction (CDP ?)
  - Metabolic enzymes : CYP ? Others ?
  - Drug transporters ?
- Potential QTc effect ?
  - Should be estimated in the worst case scenario e.g. elderly, max DDI effect, max transporter effect
- MD may target 5 to 10 fold therapeutic exposure ?

Pre-clinical signals ?

Clinical Safety Assessments

- Identify target organs in toxicology studies
  - Liver, kidneys, adrenals, heart, ...
  - Were there safety markers assessed ?
  - Was it reversible ?
  - What was the time profile after drug exposure ?
- List all potential clinical/laboratory assessments
- Plan for baseline and sufficient follow-up timepoints to observe full profile

Biomarkers ?

Clinical Safety Assessments

- Potential use/exploration of new biomarkers ?
- Preferably assessed first in animals ?
- Need for very early involvement of clinical colleagues in the drug discovery & development process (concept of «early development»)
- And remember : pharmacokinetic exposure is one of the best translational biomarker !

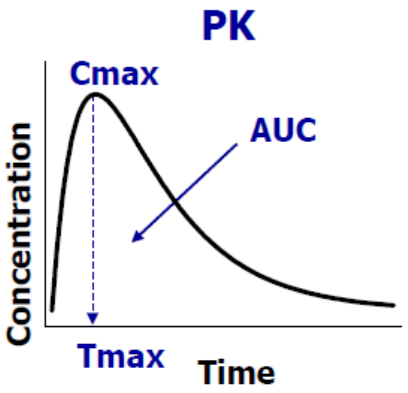
Pre-clinical signals ?

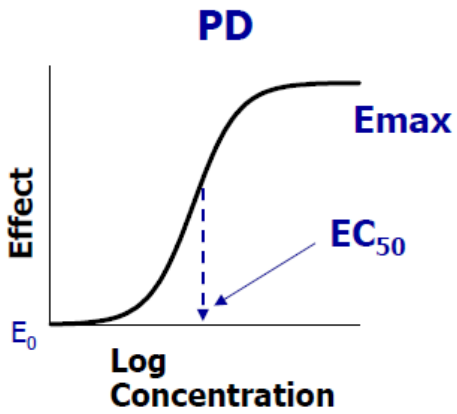
Pharmacodynamic Assessments

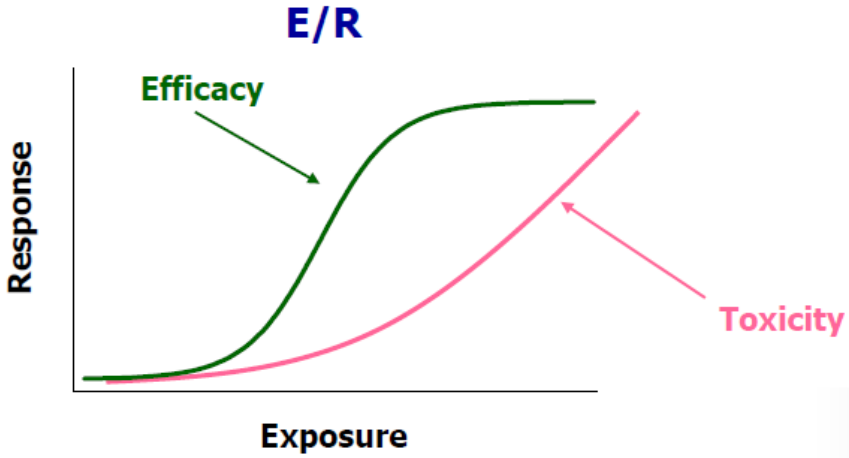
- Need to assess in animal models relevant markers of disease or of drug activity
- Need for disease models based on clinical markers
- Need for validated pharmacodynamic assays

Biomarkers ?

Pharmacodynamic Assessments







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“Good” estimates of the therapeutic dose ?

Pharmacodynamic Assessments

- Select the «right» models
  - Typically more than one model
  - Preference for chronic dosing models
  - Try to identify active concentration range
- Know the therapeutic clinical pharmacology landscape
  - Try to identify the dose/concentration/response profiles
  - Try to «guestimate» how it translates to the drug candidate
- Assess a range of exposure
  - To characterize the expected therapeutic window
  - To estimate where «MTD» should be searched

A recent good paper about FiH studies

A Brief Survey of First-in-Human Studies

David Wexler, BS, and Kirk M. Bertelsen, PhD

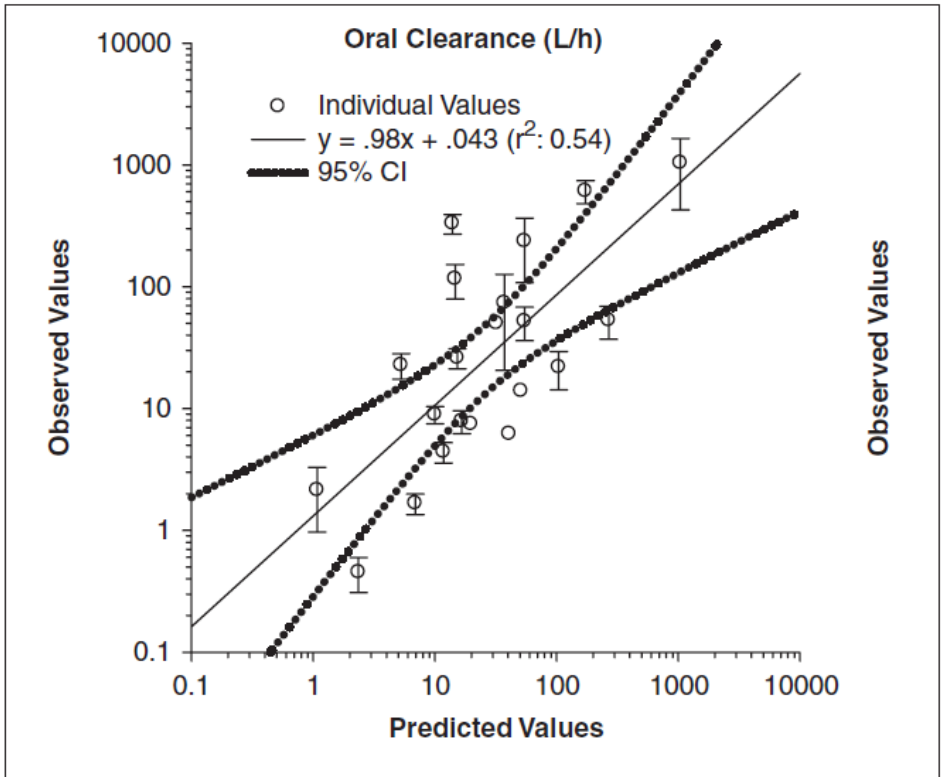
Journal of Clinical Pharmacology, 2011;51:988-993

Johnson & Johnson, Pharmaceutical Research & Development,
San Diego, California.

Table I Descriptive Parameters Describing Preclinical Toxicology and First-in-Human Study Parameters

Parameter	Median	Minimum	Maximum	n
NOAEL study dose range[a]	20.0	4.0	300	38
Applied safety factor[b]	45.2	2.3	2258	20
Cohort per study	6.0	4.0	11.0	21
FIH dose range[c]	80.0	5.0	225	21
Dose escalation per cohort	2.0	0.53	5.0	21

FIH, first-in-human; NOAEL, no observable adverse effect level.
a. Ranges calculated as the ratio of the high and low doses administered in each species.
b. Safety factor applied to human equivalent dose for the calculation of the starting dose with FIH studies.
c. Ranges calculated as the ratio of the high and low doses administered in a given FIH study.



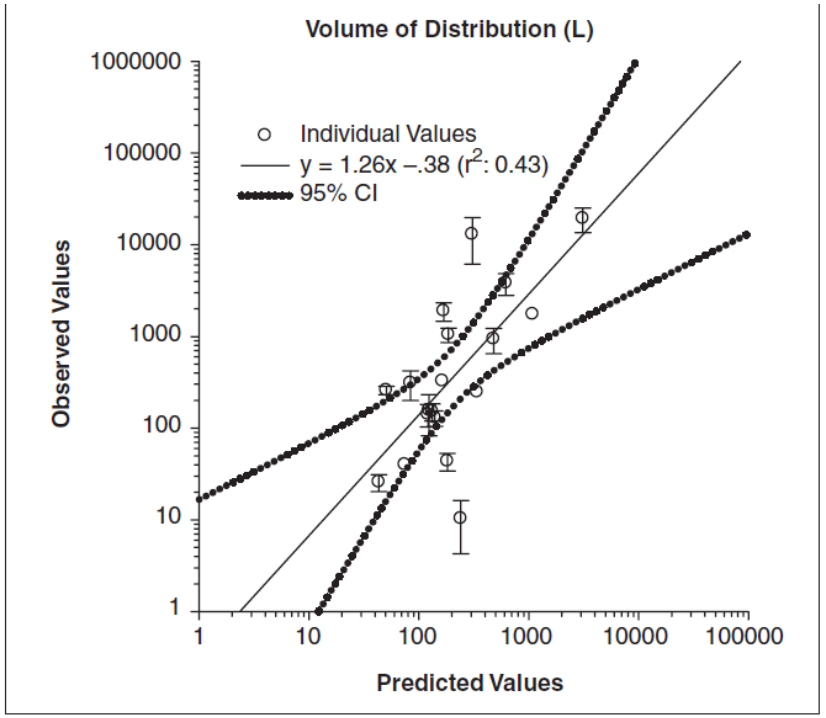


Figure 1. Observed mean (standard deviation) vs predicted values for human oral clearance (L/h) and volume of distribution (L). CI, confidence interval.

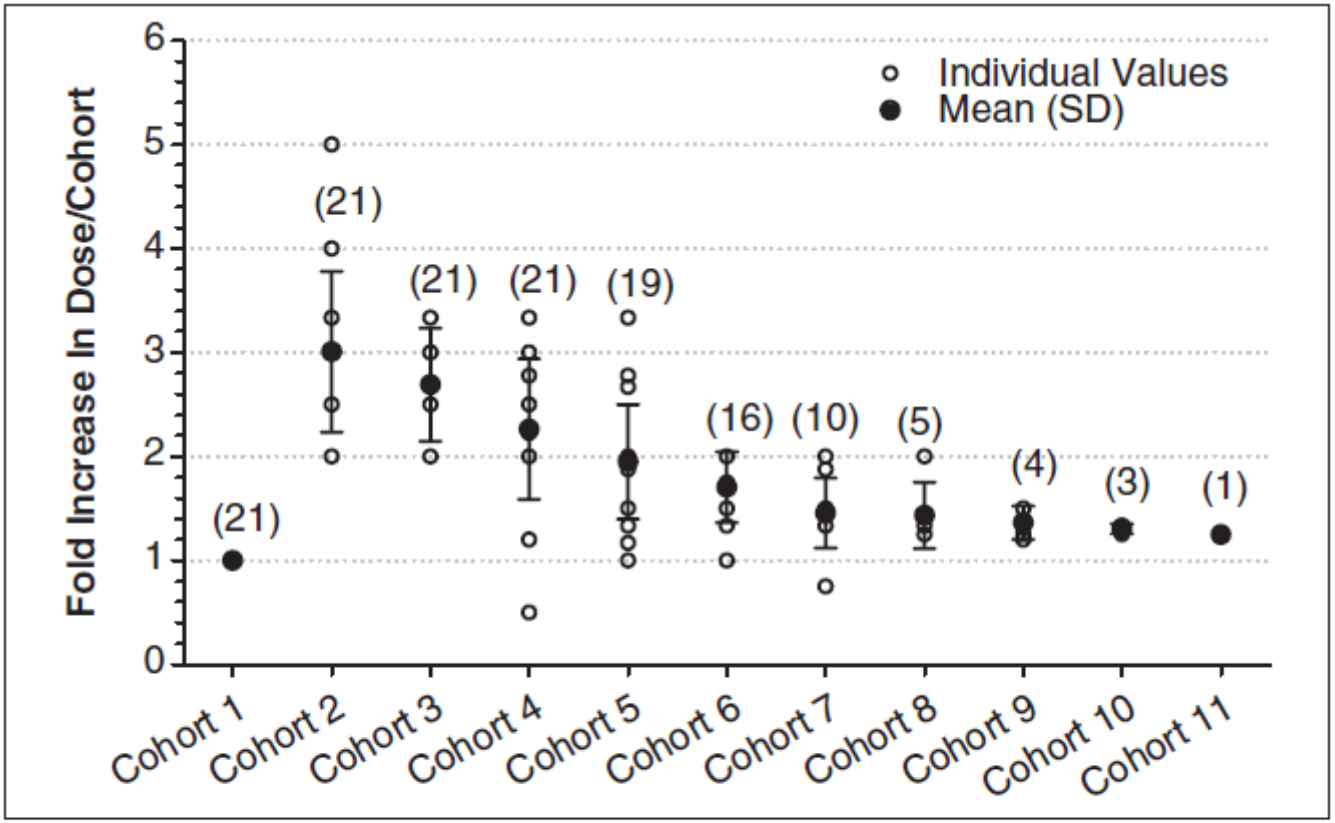


Figure 2. Mean (standard deviation [SD]) and individual dose escalations per cohort in first-in-human single ascending dose studies.

Table II Relative Comparison of Preclinical C_{max} and AUC Values at NOAEL to First-in-Human C_{max} and AUC Values at the Maximum Tolerated Dose

	Median	Minimum	Maximum	n[a]
Greater than NOAEL C_{max} values	3.0	1.2	7.7	8
Less than NOAEL C_{max} values	0.26	0.001	0.93	28
Greater than NOAEL AUC values	2.3	1.1	18.2	18
Less than NOAEL AUC values	0.20	0.001	0.81	19

AUC, area under the concentration–time curve; C_{max}, maximum concentration; NOAEL, no observable adverse effect level. Values for median, minimum, and maximum given as fold differences.

a. Count reflects the total number of species included per compound.

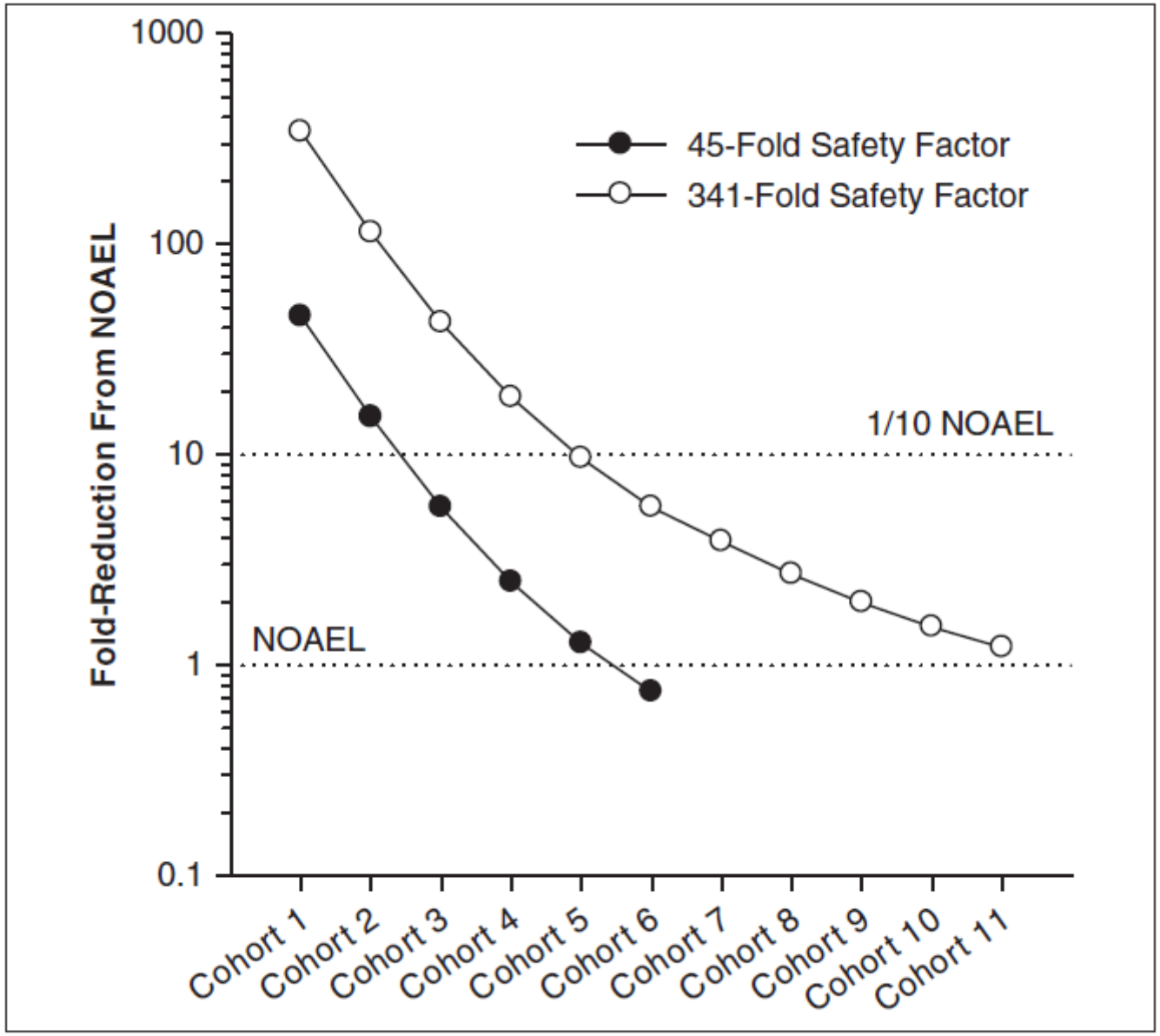


Figure 3. Effect of starting dose safety factors and dose escalation in approaching no observable adverse effect level (NOAEL) exposures.

Current thoughts on FiH with Biologics «at risk»

- SAD
  - Healthy volunteers or patients ?
  - Sentinel dosing ? For how long ?
  - Intravenous (some HA demand it) or subcutaneous route ?
- MAD
  - Is it needed ?
  - Patients ? What type of patients ?

Design a «pragmatic» but innovative study

Study phase														
Visit Numbers (internal use only)														
Day	1													
Time (h)	pre-dose	start of inj. (soi)	1 min after soi	2 min after soi	4 min after soi	end of inj. (eoi)	1 min after eoi	2 min after eoi	5 min after eoi	15 min after eoi	2	4	8	24
Obtain informed consent														
Inclusion /Exclusion criteria														
Relevant med history / current medical conditions														
Demography														
Physical examination														
Hepatitis and HIV screen														
Pregnancy test														
Urine drug screen														
Drug administration		< - - -	- - - - -	- - - - -	- - - - -	- - - >								
Study completion information														
Vital signs and body measurements														
Body height														
Body weight														
Body temperature														
Blood pressure / Pulse rate	X										X	X	X	X
ECG evaluation														
Hematology, Blood chemistry, Urinalysis														
Blood samples for PK analysis 1	X												X	
Blood samples for immunogenicity assessment	X													
(Serious) Adverse Events	< - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -
Concomitant meds/Therapies	< - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -
Injection site assessment 2						X	X	X	X	X				
100 mm VAS pain assessment 3			X	X	X	X	X	X	X	X				
Leakage assessment 4						X	X	X	X	X				
Pruritus assessment 3			X	X	X	X	X	X	X	X				
Confinement to study center 5	< - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - >
Visit to study center														

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Tentative Conclusions

Safety First !

- First dose in man protocol should :
  - Be based on preclinical data available : Translational aspect
  - Include different estimates of first dose
- Safety and pharmacodynamic assessments :
  - List based on preclinical data
  - Time to be assessed based on expected pk profile in man
- Working document concept
  - Team collaboration
  - Adaptive design

Thank you for your attention

- Any Questions ?

Back-Up Slides

References

- M3 (R2) guidance
  http://www.ich.org/products/guidelines/safety/safety-single/article/guidance-on-nonclinical-safety-studies-for-the-conduct-of-human-clinical-trials-and-marketing-author.html
- EMA guidance
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf
- FDA guidance
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078932.pdf

Te Genero Example : The TGN1412 humanised monoclonal antibody

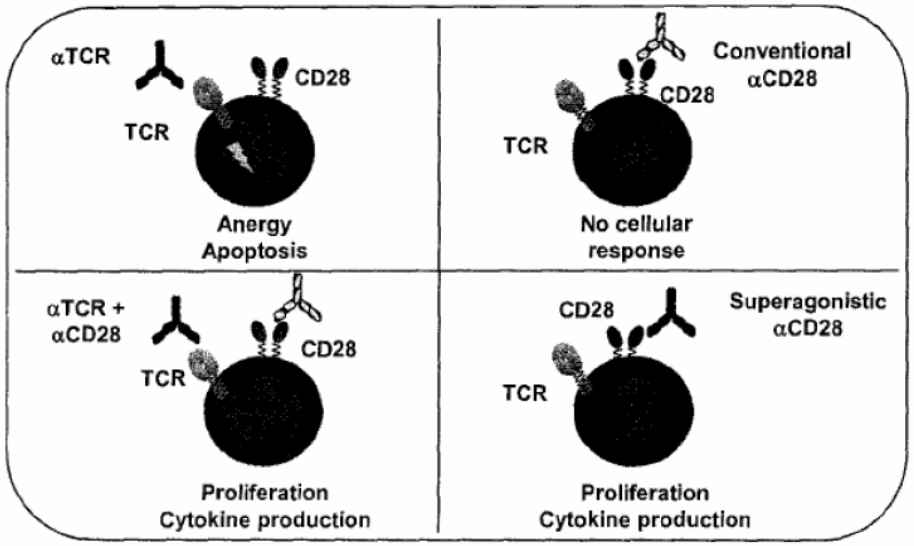
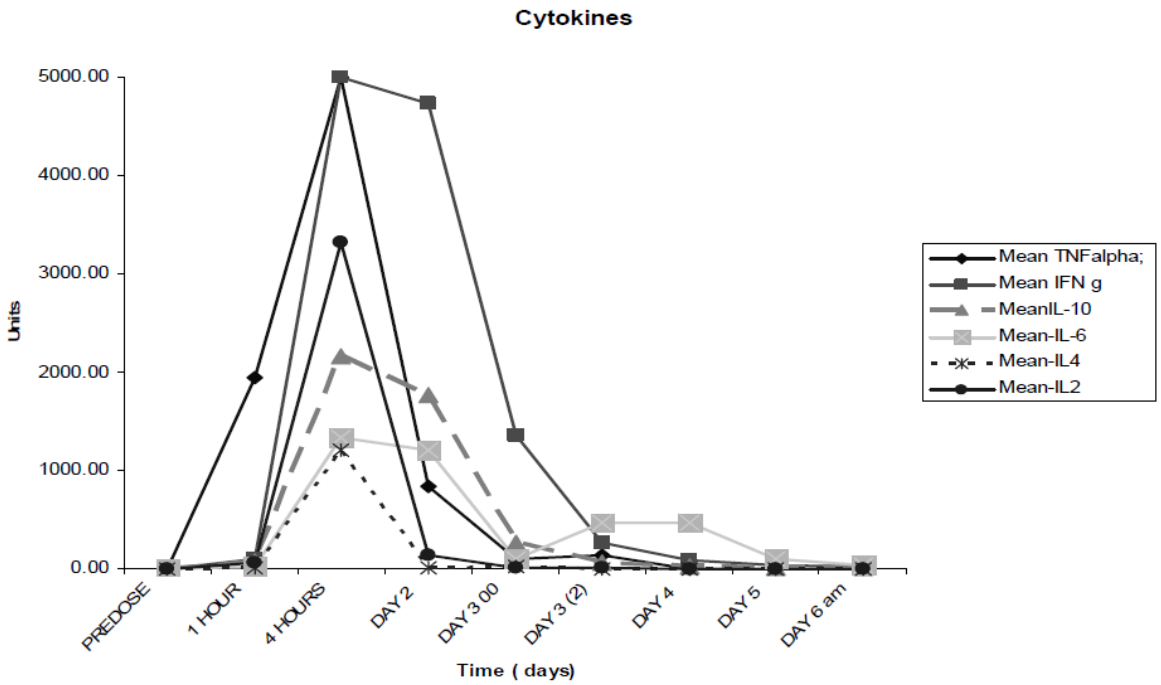


Figure 1: Activation of human T cells in the absence of TCR stimulation TGN1412 bypasses the requirement for TCR signalling triggering and activates human T cells in the absence of TCR stimulation . In T cells, TCR triggering alone leads to anergy and apoptosis. Conventional anti-CD28 antibodies are not capable of inducing cellular T cell response. Concomitant triggering *via* anti-TCR and anti-CD28 antibodies leads to proliferation and secretion of pro-inflammatory cytokines *in-vitro*, but not *in vivo*. In contrast, TGN1412 induces profound *in vitro* T cell proliferation and well-tolerated *in vivo* expansion of T cells.

Cytokine Release Syndrom



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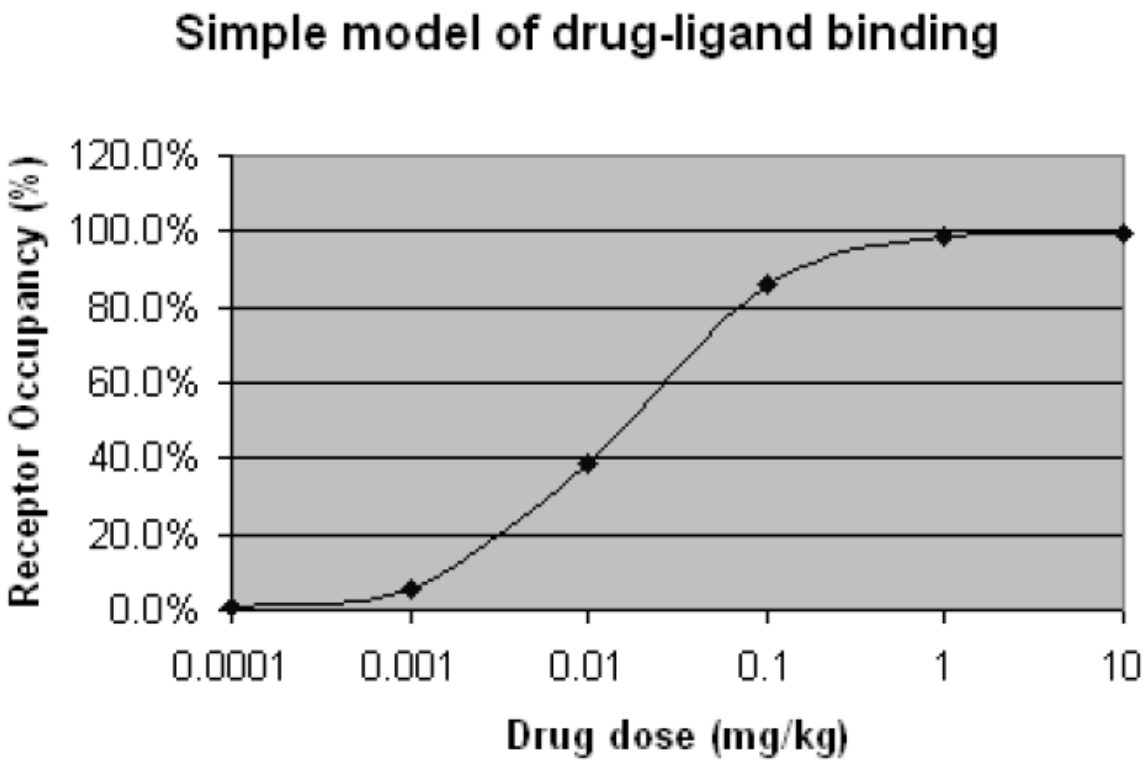
Receptor Occupancy for TGN1412 as calculated by the ABPI/BIA Taskforce

- Dose TGN1412 : 0.1 mg/kg
- Body weight : 70 kg
- Molecular weight TGN1412 : 150000
- Blood volume 5L and plasma volume 2.5L
- T lymphocyte count at baseline (before dosing) = 1.3 x 10^9 cells per L blood
- CD28 receptors per Tcell 150000 (Bryl et al 2001; 167 (6): 3231-3238)
- Kd 1.88 nM (TeGenero, information in public domain)
- Total TGN1412 concentration (A + C) in plasma immediately post-dosing 18.7 nM
- Total ligand (CD28) concentration (B + C) exposed to plasma at baseline 0.648 nM,
- assuming B + C = 1.3 x 10^9 x 150,000 (receptors/cell)/*NA* x 10^9
- Drug-ligand concentration (C) immediately post-dosing 0.587 nM
- **Percentage CD28 receptors occupied by TGN1412 : 90.6%**

Calculated receptor occupancy of TGN1412



Starting dose : 0.1 mg/kg

Safety Factor

FDA guidance on starting dose

- The safety factor provides a margin of safety for protection of human subjects receiving the initial clinical dose
- The default safety factor is usually 10
- Allows for variability in extrapolating from animal toxicity studies to studies in humans
  - Uncertainties due to enhanced sensitivity in humans vs. animals
  - Difficulty in detecting certain toxicities in animals (Headache, myalgia)
  - Differences in receptor densities or affinities
  - Unexpected toxicities
  - Interspecies difference in absorption, distribution, metabolism, excretion (ADME)

Increasing the Safety Factor

FDA guidance on starting dose

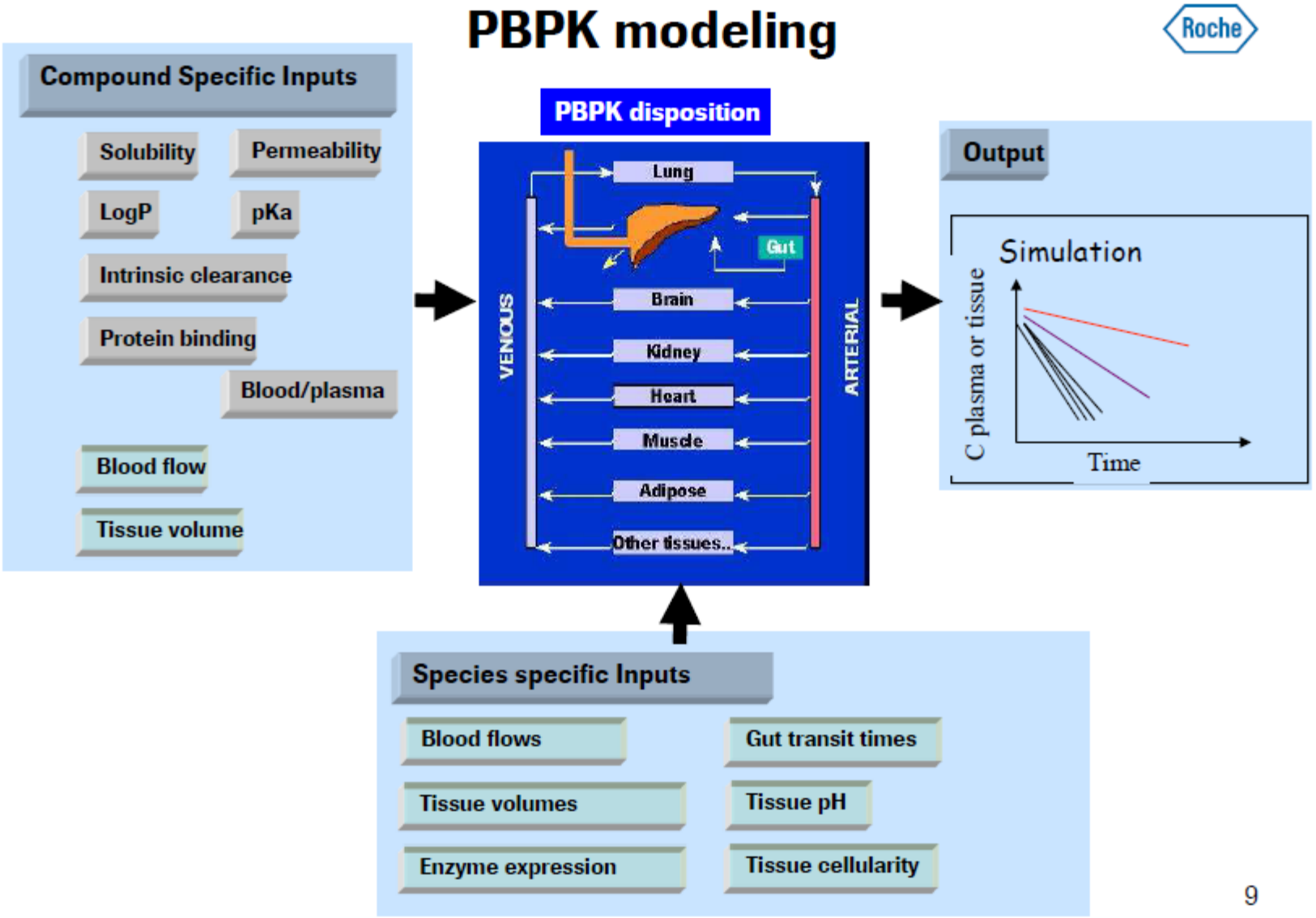
- Novel therapeutic class
- Toxicities:
  - Severe or irreversible
  - Nonmonitorable toxicity- histopathologic changes in animals, not readily monitored clinically/markers
- Steep dose response curve
  - May indicate a greater risk in humans
- Non-linear pharmacokinetics:
  - Limits the ability to predict dose-related toxicity
- Variable bioavailability
  - Poor bioavailability in test species may underestimate toxicity in humans

Decreasing the Safety Factor

FDA guidance on starting dose

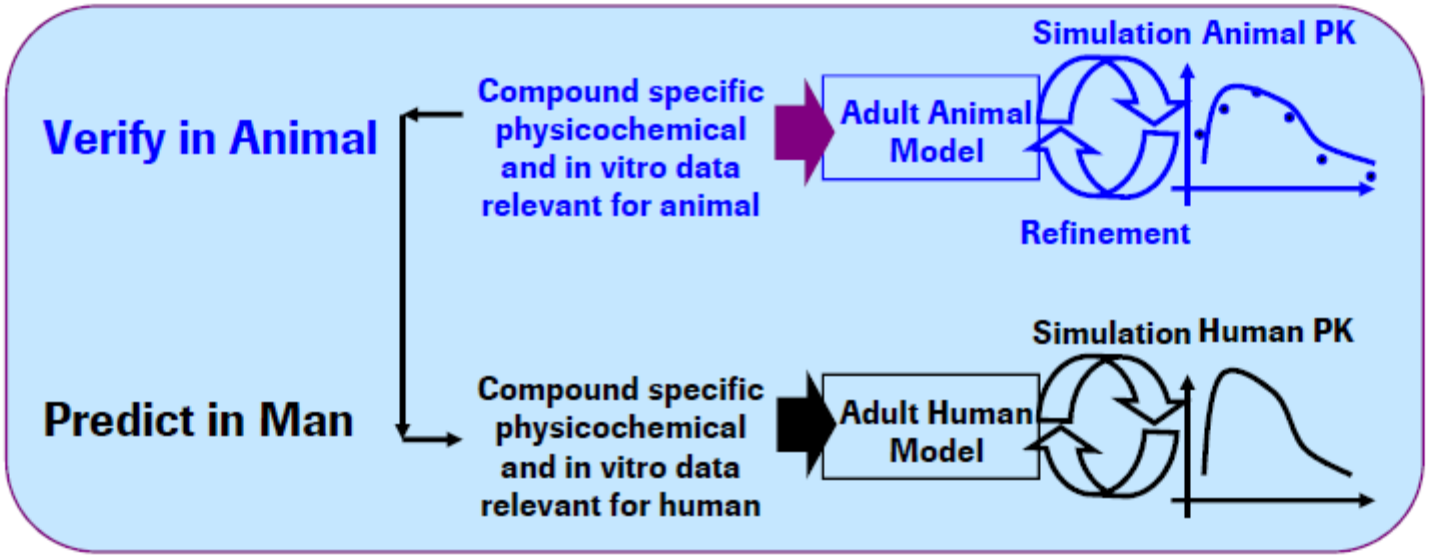
- Members of a well-characterized class
- Toxicities produced by the therapeutic agent are easily monitored, reversible, predictable
- If the NOAEL was determined based on toxicity studies of longer duration
  - assuming toxicities are cumulative
  - are not associated with acute peaks in therapeutic concentration, and
  - did not occur early in the repeat dose study

PBPK modeling



Roche PBPK strategy

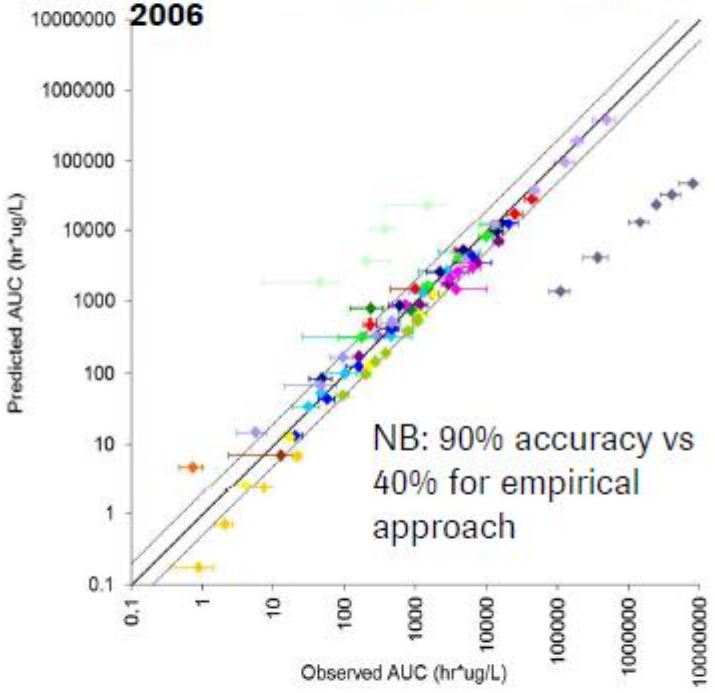
- *In vivo* animal data used to verify preclinical predictions
- Mismatch of simulations to in vivo data prompt additional experiments
- Ability to simulate in animals determines confidence in human prediction



Overarching goal is to predict therapeutic window in humans as a function of dose using a PBPK/PD approach

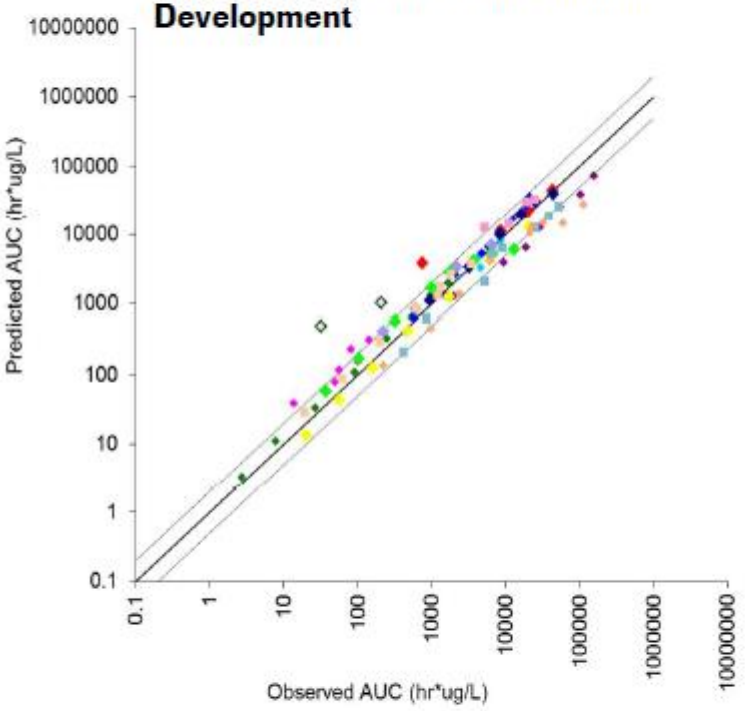
PBPK clinical predictions for Roche molecules

Jones et al. Clinical Pharmacokinetics, 2006



N=17
Ave. fold error 2.6
76% within 2-fold

Recent Roche entries into Clinical Development



N=16
Ave. fold error 1.8
75% within 2-fold

BIA 10-2474

- All developed FAAH inhibitors : formation of a covalent bond between hydrolase serine 241 and the carbamate or urea electrophilic carbon.
- FAAH inhibition therefore considered to be irreversible.
- According to Bial, BIA 10-2474 is effectively covalently bound to FAAH (therefore irreversibly) in vitro but partially reversibly in vivo. Already been reported in the case of Janssen & Janssen's inhibitor (JNJ-42165279) with which partial enzyme activity is observed after 8 hours.
- Low specificity for its target enzyme :
  - Concentrations inhibiting FAAH activity at 50% (IC50) range,
  - 1.7 (1.5 – 1.9) µM in mice
  - 1.1 (0.9 – 1.3) µM in rats.
  - 100 times higher at most for the various other enzymes against which BIA was tested

Other Compounds

- PF-04457845 (Pfizer)
  - tested against 68 receptors
  - IC50 of 7.2 nanomolar (nM) for human FAAH
  - 240 times lower than that of BIA 10-2474
  - over 100 µM for a panel of around twenty hydrolases.
  - Specificity ratio of Pfizer's compound : ~ 14,000 (BIA ~100)
- JNJ-42165279 (Janssen)
  - tested on 50 enzymes
  - IC50 of 70nM
  - developed for the treatment of anxiety and major depressive disorder

BIA 10-2474 Preclinical pharmacodynamic data

- Relatively weak activity
  - 50% FAAH inhibition in vitro : µM range
  - IC50 of BIA 10-2474 for FAAH ~ 240 times higher than PF-04457845
- Low specificity
  - In vitro inhibition of other enzymes at concentrations 50 to 100 times those inhibiting FAAH
- Very steep dose-effect curve slope
- Long-acting
  - In humans, inhibition over 24 hours, whereas BIA plasma concentrations below the limit of quantification of the test method used

Animal toxicology data

- The NOAEL for the 4-week and 3-month studies are respectively:
  - 100 and 25 mg/Kg/24h in mice,
  - 30 and 10 mg/Kg/24h in rats,
  - 50 and 20 mg/Kg/24h in dogs,
  - 100 and 75 mg/Kg/24h in monkeys.
- On the bases of the calculated NOAEL, and by referring to Food and Drug Administration (FDA) procedures, it was in theory logical to test a dose of up to 100 mg in humans (96 mg according to the TSSC's calculation).

Clinical trial conducted in Rennes by Biotrial

BIA 10-2474

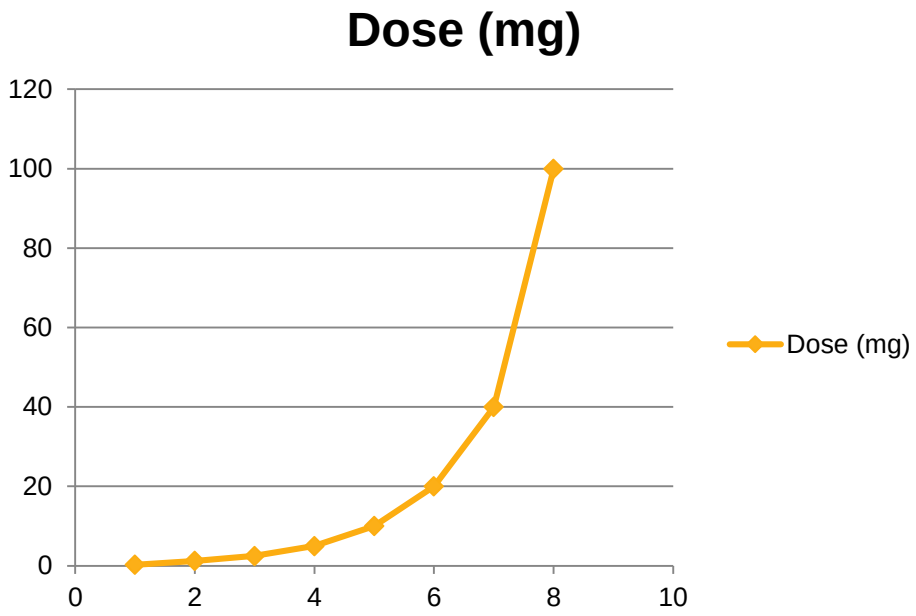
- Phase 1, monocentric, First-in-Human (FIH) trial planned to include 128 healthy male and female volunteers in total, aged 18 to 55 years, and involved four parts:
  - single ascending dose (SAD) study,
  - multiple ascending dose (MAD) study,
  - food interaction open study, and
  - pharmacodynamics study (not done).
- “The choice of the first dose administered (0.25 mg) was careful for the SAD part, as it was equivalent to around 1/400th of the highest dose with no observable adverse effect level (NOAEL) in animals”

BIA-102474-101 clinical trial

SAD part

- 64 volunteers in 8 cohorts of 8 volunteers :
  6 receiving the active treatment and 2 the placebo

- Dose levels :
  - 0.25 mg
  - 1.25 mg
  - 2.5 mg
  - 5 mg
  - 10 mg
  - 20 mg
  - 40 mg
  - 100 mg



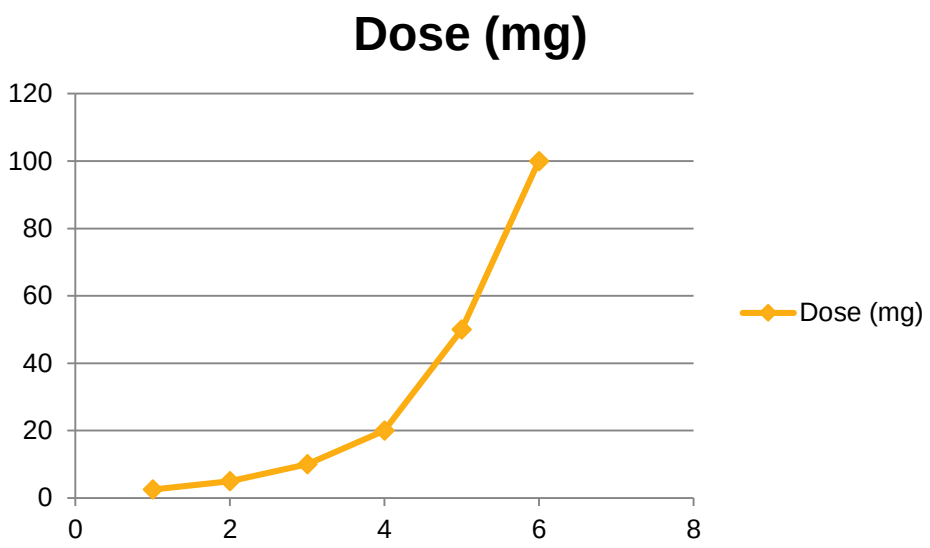
NOVARTIS

BIA-102474-101 clinical trial

MAD part

- 48 volunteers in 6 cohorts of 8 volunteers :
  6 receiving the active treatment and 2 the placebo

- Dose levels planned :
  - 2.5 mg qd for 10 days
  - 5 mg qd for 10 days
  - 10 mg qd for 10 days
  - 20 mg qd for 10 days
  - 50 mg qd for 10 days
  - 100 mg qd for 10 days
  - From the 10 mg dose, administration was based on the pharmacokinetic data measured at n-2 (i.e. that for the 10 mg cohort to start administration of 50 mg)



BIA-102474-101 clinical trial

Food interaction part

- The food interaction study involved 12 volunteers at the 40 mg dose

Chronological events

- MAD cohort 5 at 50 mg qd began on 6 January 2016 (D1)
- Evening of Day 5 (10-Jan-2016) : One subject hospitalized (SAE)
- Day 6 morning (11-Jan) : 5/6 subjects received a 6th dose
- Day 6 noon : decision to stop study treatment
  2 other volunteers hospitalized
- Day 7 (12-Jan) : 2 other volunteers hospitalized
- Day 8 (13-Jan) : 1 other volunteer (last active) hospitalized

Clinical symptoms

- Headaches, in all five volunteers, very severe in one but not occurring as a thunder clap headache,
- Cerebellar syndrome in three volunteers,
- Consciousness disorders (in three volunteers) ranging from sedation to coma (deceased volunteer),
- Memory impairment in two volunteers.

ILLUSTRATION BY RICHARD WILKINSON

Consider drug efficacy before first-in-human trials

JUDGING DRUG EFFICACY

Three questions to assess clinical promise

Ethics requires clear-eyed evaluation of a drug's potential. These questions can help provide clarity.

What is the likelihood that the drug will prove clinically useful?

- How have other drugs in the same class or against the same target performed in human trials?
- How have other drugs addressing the same disease process fared?

Assume the drug works in humans. What is the likelihood of observing the preclinical results?

- Are the treatment effects seen in animals large and consistent enough to suggest a tangible benefit to patients?
- How well do animal models reflect human disease?

Assume the drug does not work in humans. What is the likelihood of observing the preclinical results?

- Have effects of random variation and bias been minimized (for example by sample sizes, randomization, blinding, dose-response curves and proper controls)?
- Do the conditions of the experiment (for instance age of animal models, timing of treatments and outcomes) match clinical scenarios?
- Have effects been reproduced in different models and/or in independent laboratories?