Usefulness of MABEL concepts

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clinical pharmacology
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What is MABEL?

Minimum Anticipated Biological Effect Level

In Humans!

"[*For a biological product*], *the estimation of the dose or exposure required at the bottom end of the dose response curve in man is more important than NOAEL. This might be termed the Minimum Anticipated Biological Effect Level (MABEL).*"

Early Stage Clinical Trial Taskforce, Joint ABPI/BIA Report, July 2006

A Phase I , single-centre, double-blind, randomised, placebo-controlled, single escalating-dose study to assess the safety, pharmacokinetics, pharmacodynamics and immunogenicity of TGN1412, administered intravenously to healthy volunteers

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From The Times
March 16, 2006

'Test turned into a living hell minutes after we were injected'

By Ian Evans

ONE of the two volunteers given a placebo in the drugs test last night told how he witnessed the collapse of the other trialists shortly after they had taken the drug.

"The test ward turned into a living hell minutes after we were injected. The men went down like dominoes," Raste Rhan, 23, a television technican, said.

"First they began tearing their shirts off, complaining of fever, then some screamed out that their heads felt like they were about to explode," he said. "After that they started fainting, vomiting and writhing around in their beds. It was terrifying because I kept expecting it to happen to me at any moment. But I felt fine and didn't know why," he told The Sun.

"An Asian guy next to me started screaming and his breathing went haywire as though he were having a terrible panic attack. They put an oxygen mask on him, but he kept tearing it off, shouting: 'Doctor, doctor, please help me!' He started convulsing, shouting that he was getting shooting pains in his back."

Mr Khan said that the men had all turned up on Sunday and slept the night on what appeared to them to be a private ward.

The volunteers were given extensive tests to check that they were in good general health before the tests could go ahead.

The next morning the men had needles inserted into both arms, Mr Khan said. "The needles had sort of valve devices so they could inject drugs and take our blood for tests," he said.

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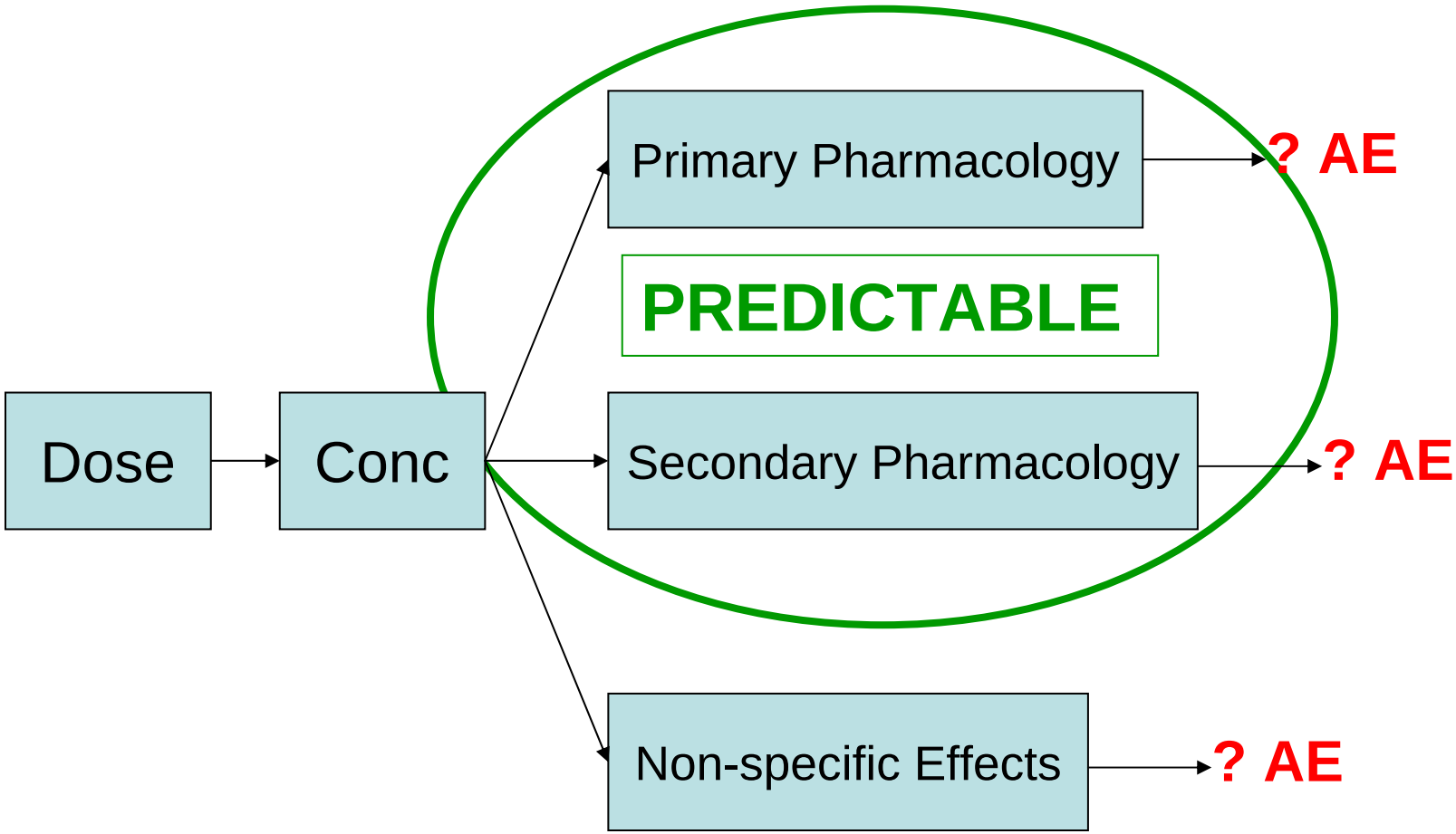
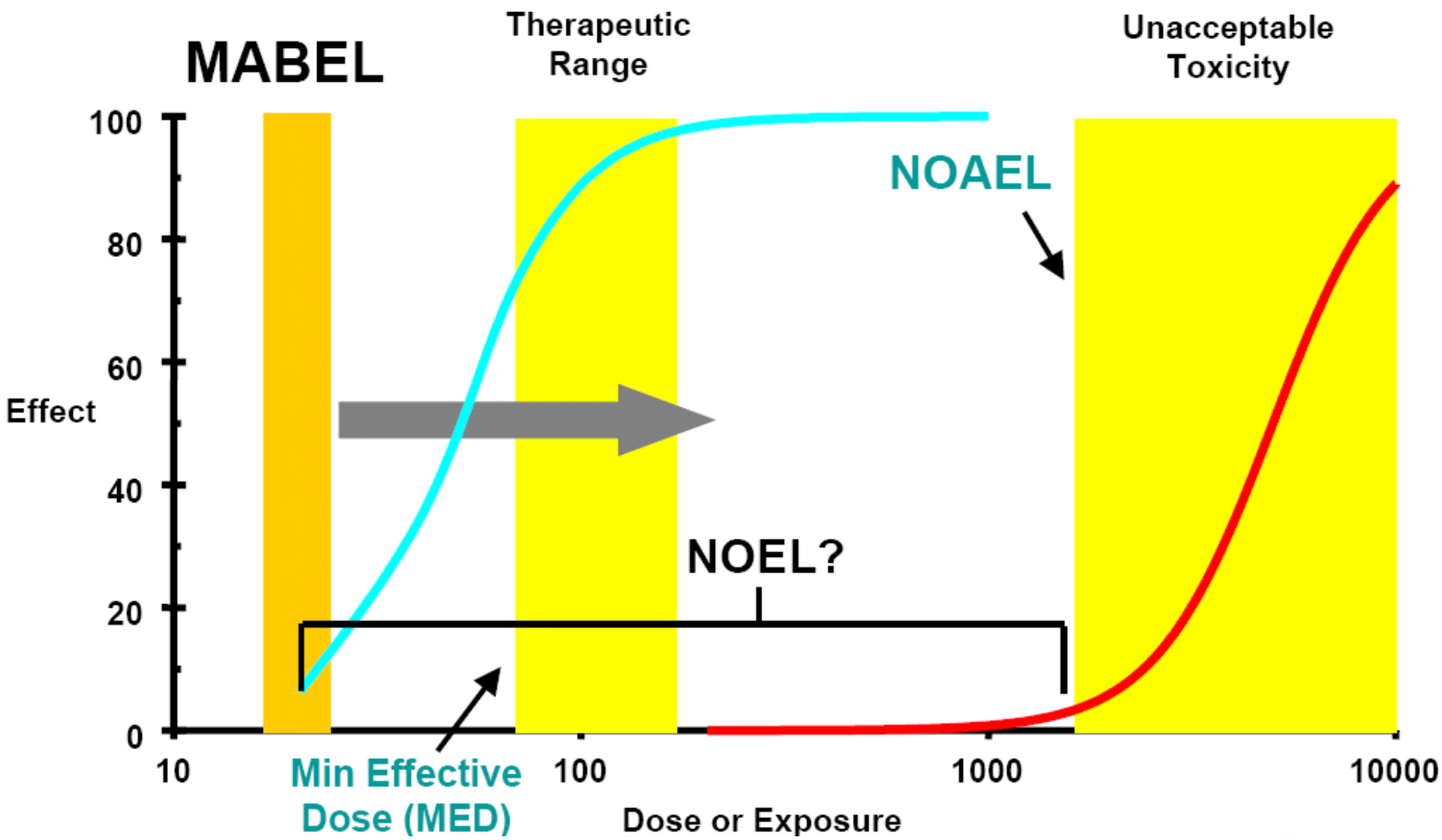
What constitutes Safety?

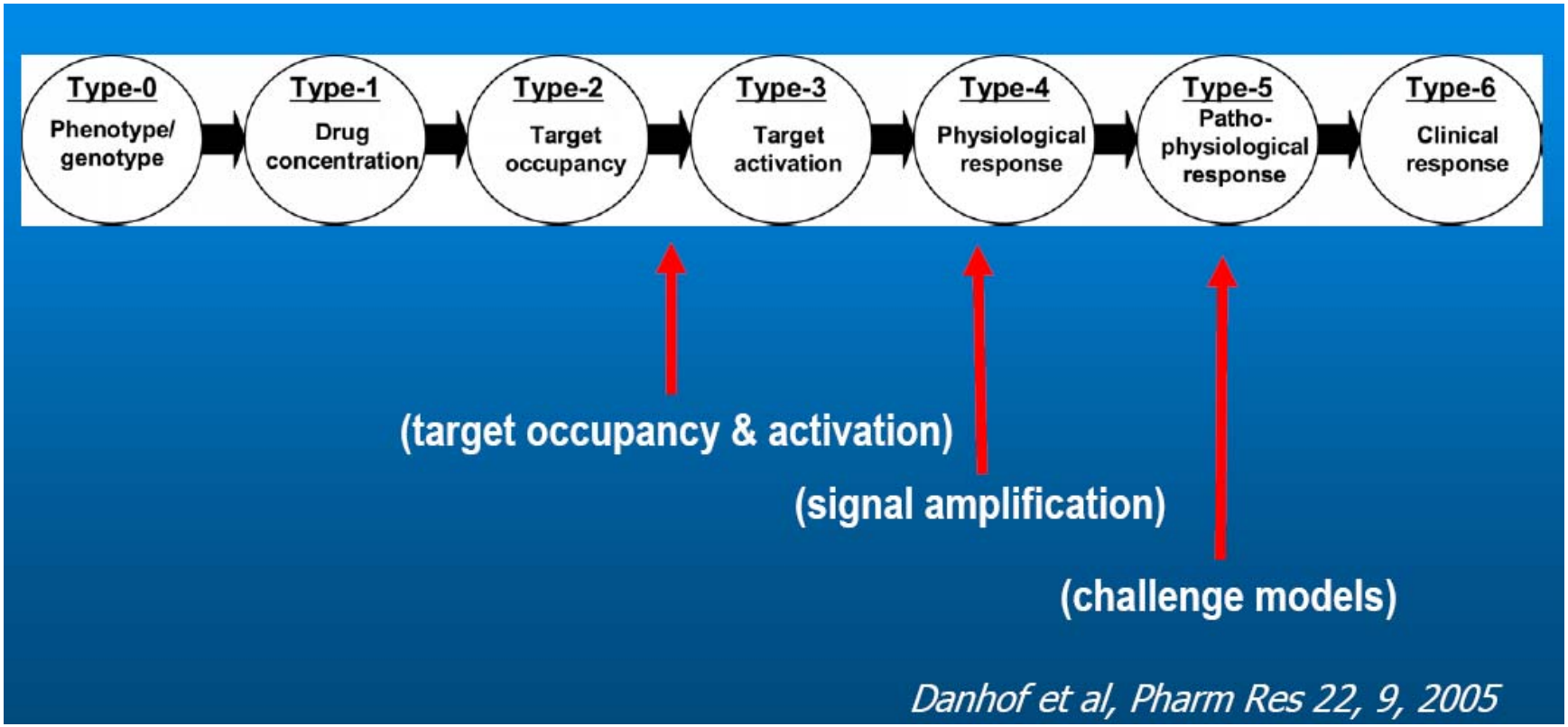


Pharmacology & Toxicology



[Jennifer Sims, ABPI/BIA Early Clinical Trials Taskforce, slideset]

Mechanistic Classification of Biomarkers



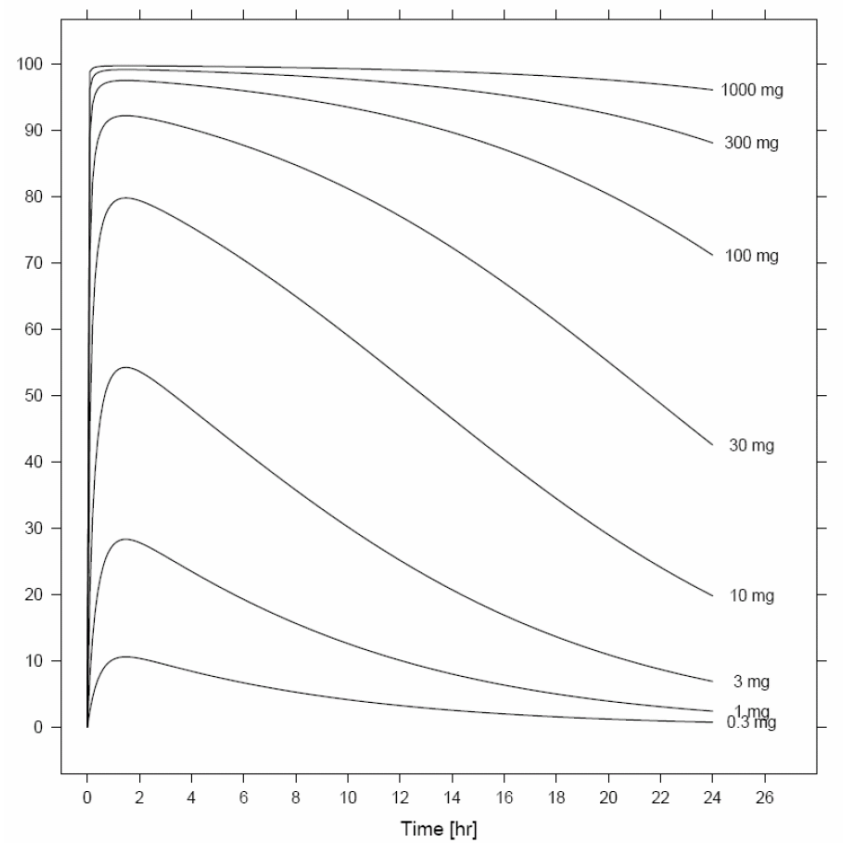
How to Predict a Dose with Minimal Pharmacology?

- Distribution to target(s) in Humans:
  - Transporters (eg PgP)
  - Extracellular vs Intracellular target
- Interaction with the Human Target(s)
  - Affinity (in vitro, ex vivo)
  - Efficacy (agonism vs antagonism)
- Human pharmacology
  - In vitro, ex vivo
  - Animal models of physiology (or Disease)
  - Direct vs Indirect effects
- Knowledge
  - Experience with mechanism in Humans
  - Human physiology
  - General Pharmacological Theory

An example

Dose	AUC(0-∞)	Cmax	Max Inhibition	NOAEL AUC ratio	NOAEL Cmax ratio
[mg]	[µg*hr/ml]	[µg/ml]	[%]		
0.3	0.034	0.004	11	2126	4440
1	0.134	0.012	28	638	1332
3	0.340	0.036	54	213	444
10	1.134	0.119	80	64	133
30	3.401	0.356	92	21	44
100	11.34	1.186	98	6.4	13.3
300	34.01	3.559	99	2.1	4.4
1000[1]	113.4	11.86	~100	0.6	1.3
2000[1]	226.8	23.72	~100	0.3	0.7
3000[1]	340.1	35.59	~100	0.2	0.4

1. These doses are for illustrative purposes only. Actual exposures will not exceed the PK stopping criteria listed in Section 4.6 Dose Adjustment/Stopping Criteria of the protocol.



Biologics vs NCEs

- No liver metabolism (hence no active metabolites)
- Highly (species) specific for the target
- High affinity (target mediated disposition)
- Limited off target effects
- Most AEs through Primary Pharmacology!

Mechanism of Action of TGN1412

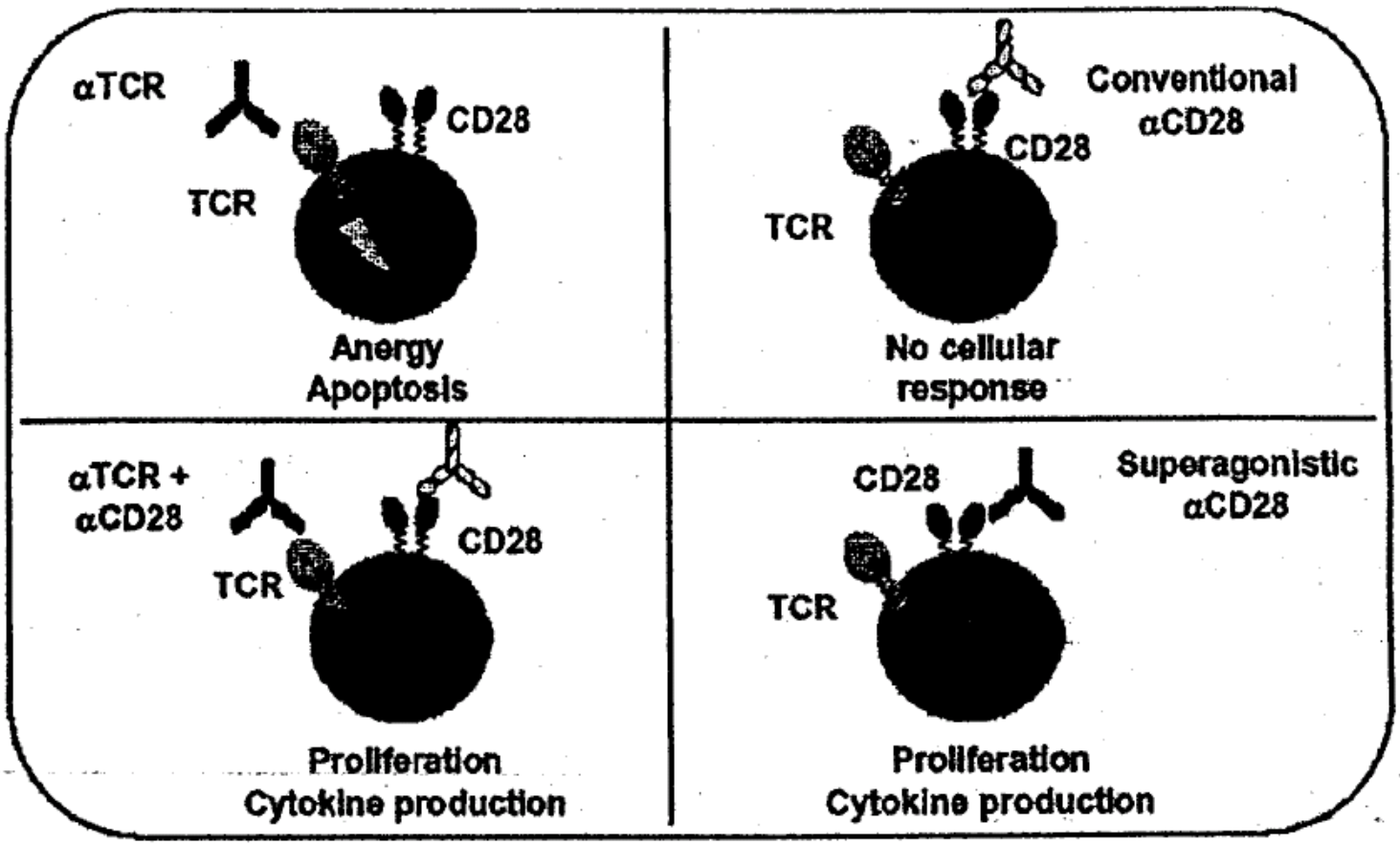


Figure 1: EudraCT no. 2005-003371-21
Parexel Study code: 68419

Dose Rational from the Protocol

3.2. Dose Rationale

A number of safety and efficacy studies with TGN1412 in non-human primates have been conducted using single- and multiple-dose regimen. The results of these studies showed that intravenous infusion (1-h infusion) of TGN1412 to cynomolgus monkeys at dose levels up to 50 mg/kg for at least four consecutive weeks were well tolerated. No TGN1412-related signs of toxicity, hypersensitivity or generalised immune system suppression were observed in these studies. Therefore, a dose level of 50 mg/kg body weight was considered the no-observed-adverse-effect level (NOAEL).

Based on a NOAEL of 50 mg/kg body weight, the clinical starting dose of 0.1 mg/kg body weight represents a 500-fold safety margin, which is considered sufficient by the company to ensure patient safety. The maximum dose in this clinical trial is 5.0 mg/kg body weight, still being 10-fold lower than the observed NOAEL in pre-clinical toxicology studies.

Pharmacological activity of agonistic anti-CD28 monoclonal antibodies has been determined in rodents and non-human primates at doses between 0.3 and 5.0 mg/kg body weight. Therefore, pharmacological activity of TGN1412 in humans may be expected in this dose range.

EudraCT no. 2005-003371-21
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Receptor Occupancy of TGN1412 at starting Dose

Dose 0.1mg/kg = 7 mg
MW 150,000
plasma volume 2.5L

Tcell 1.9 x 10^6 mL^{-1}
CD28 / cell 150,000

TGN1412 = 18.7 nM
(immediately post-dose)

CD28 = 0.95 nM
at baseline

CD28-TGN1412 = 0.86 nM
at equilirium

90% receptor occupancy

[Jennifer Sims, ABPI/BIA Early Clinical Trials Taskforce, slideset]

Conclusion

- Pharmacology
- Human! Pharmacology
- Case by Case
- Guidelines are Guidelines

Mabel concept Useful?