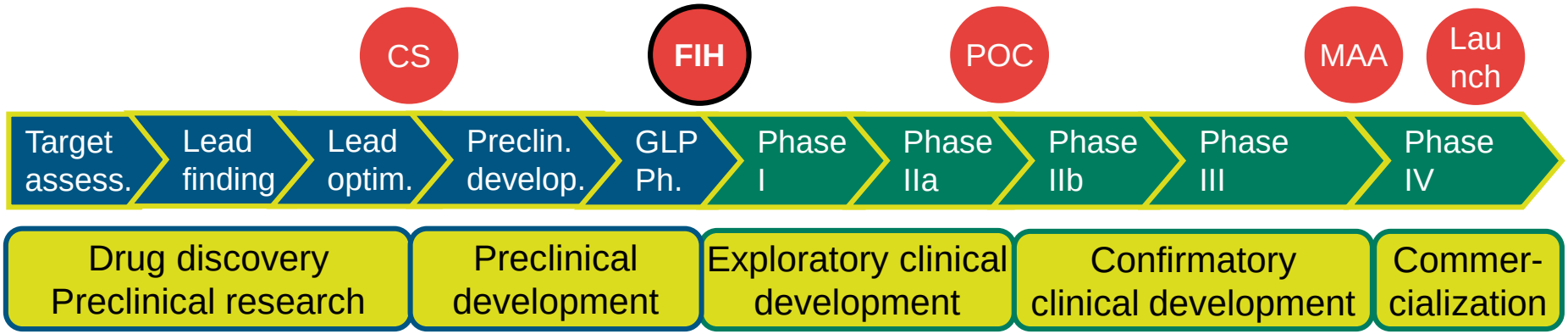
What is a first-in-human trial and what is so special about it?

Jens Rengelshausen | 28 February 2018

Content

What is a first-in-human trial?



- The purpose of a **first-in-human trial** is:
  - to evaluate an investigational medicinal product (IMP) in humans **for the first time**,
  - to study the human pharmacology, tolerability and safety of the IMP,
  - to compare how effects seen in non-clinical studies translate into humans.

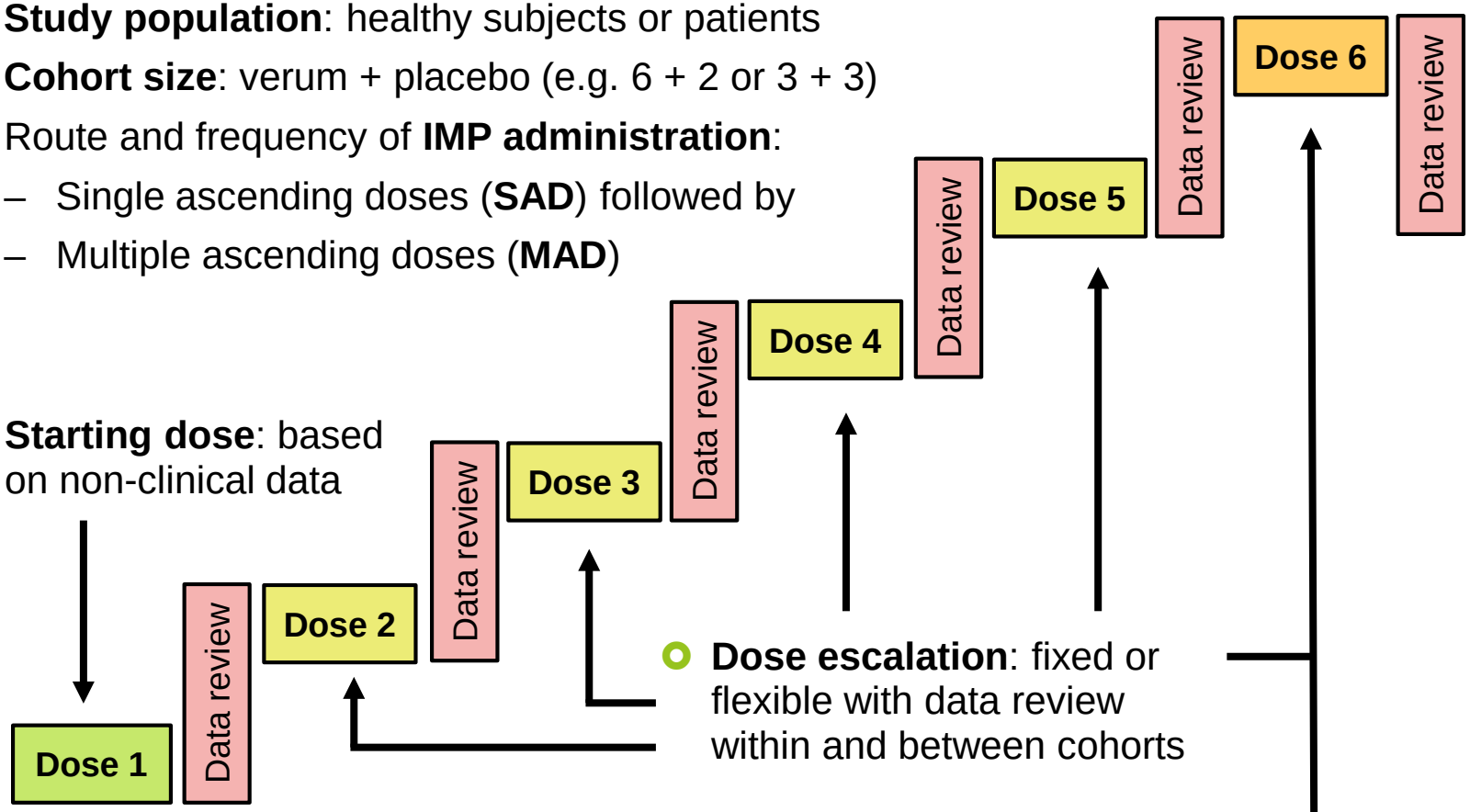
- The **safety and well-being** of trial subjects should always be the priority.

- Special consideration should be given to **characterizing risk** and putting in place appropriate strategies to **minimise risk**.

From: EMEA/CHMP/SWP/28367/07 Rev. 1; 20 July 2017

Design principles for a first-in-human trial

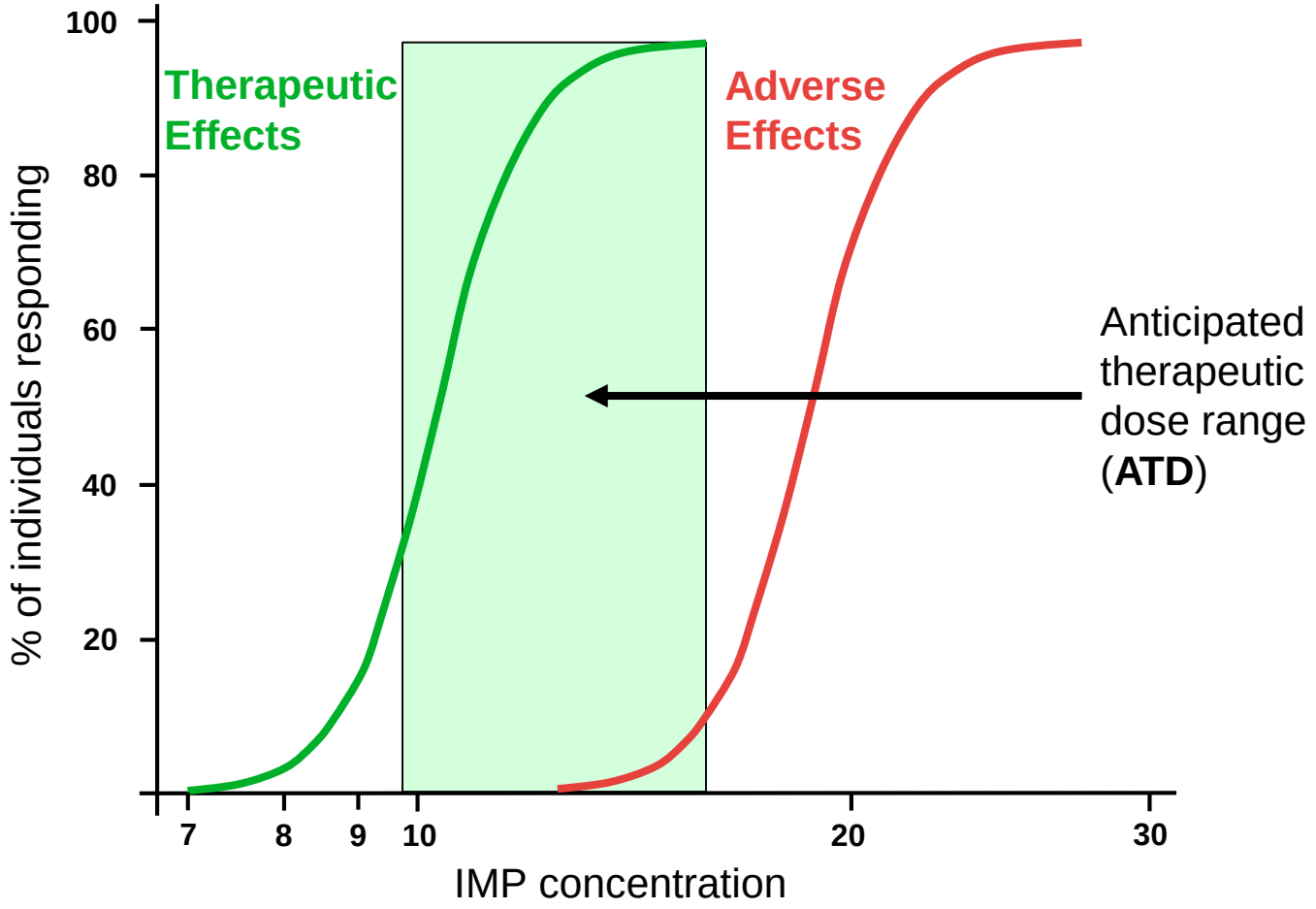
- **Study population**: healthy subjects or patients
- **Cohort size**: verum + placebo (e.g. 6 + 2 or 3 + 3)
- Route and frequency of **IMP administration**:
  - Single ascending doses (**SAD**) followed by
  - Multiple ascending doses (**MAD**)



- **Starting dose**: based on non-clinical data
- **Dose escalation**: fixed or flexible with data review within and between cohorts
- **Maximum exposure**: to be pre-defined as stopping rule

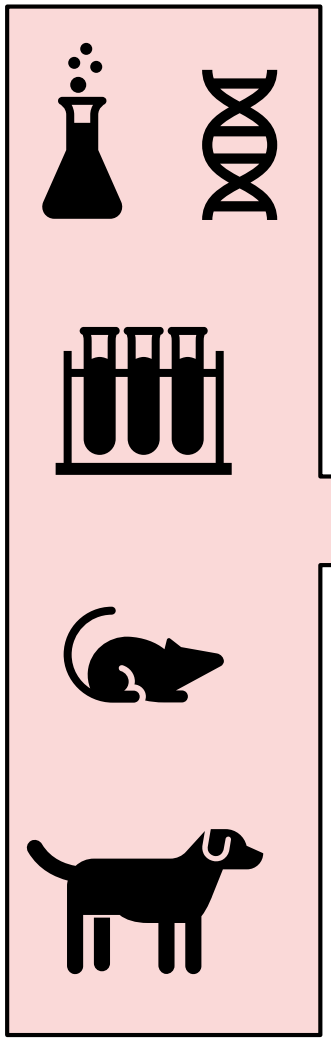
From: EMEA/CHMP/SWP/28367/07 Rev. 1; 20 July 2017

Dose – concentration – effect relationship of an IMP



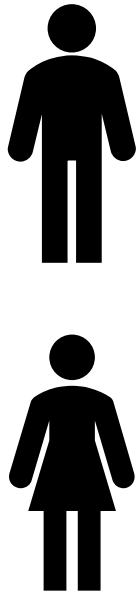
Cave: Variability of relationships: dose => concentration => effect

Basis for first-in-human trial: translation of non-clinical data



- **Translation of (human) in vitro data, e.g.:**
  - Target binding and functional interaction
  - Impact of target polymorphisms
  - Off-target binding and effects
  - Safety pharmacology and toxicology
  - Metabolism and transporter interactions

Allometric scaling / PB-PK / PK-PD modelling



- **Translation of in vivo animal data, e.g.:**
  - Primary + secondary pharmacodynamics
  - Safety pharmacology and toxicology
  - Pharmacokinetics (ADME) and toxicokinetics
- **Cave:** relevance of animal model + species
  - Target expression and functional effects
  - Pharmacodynamics and pharmacokinetics

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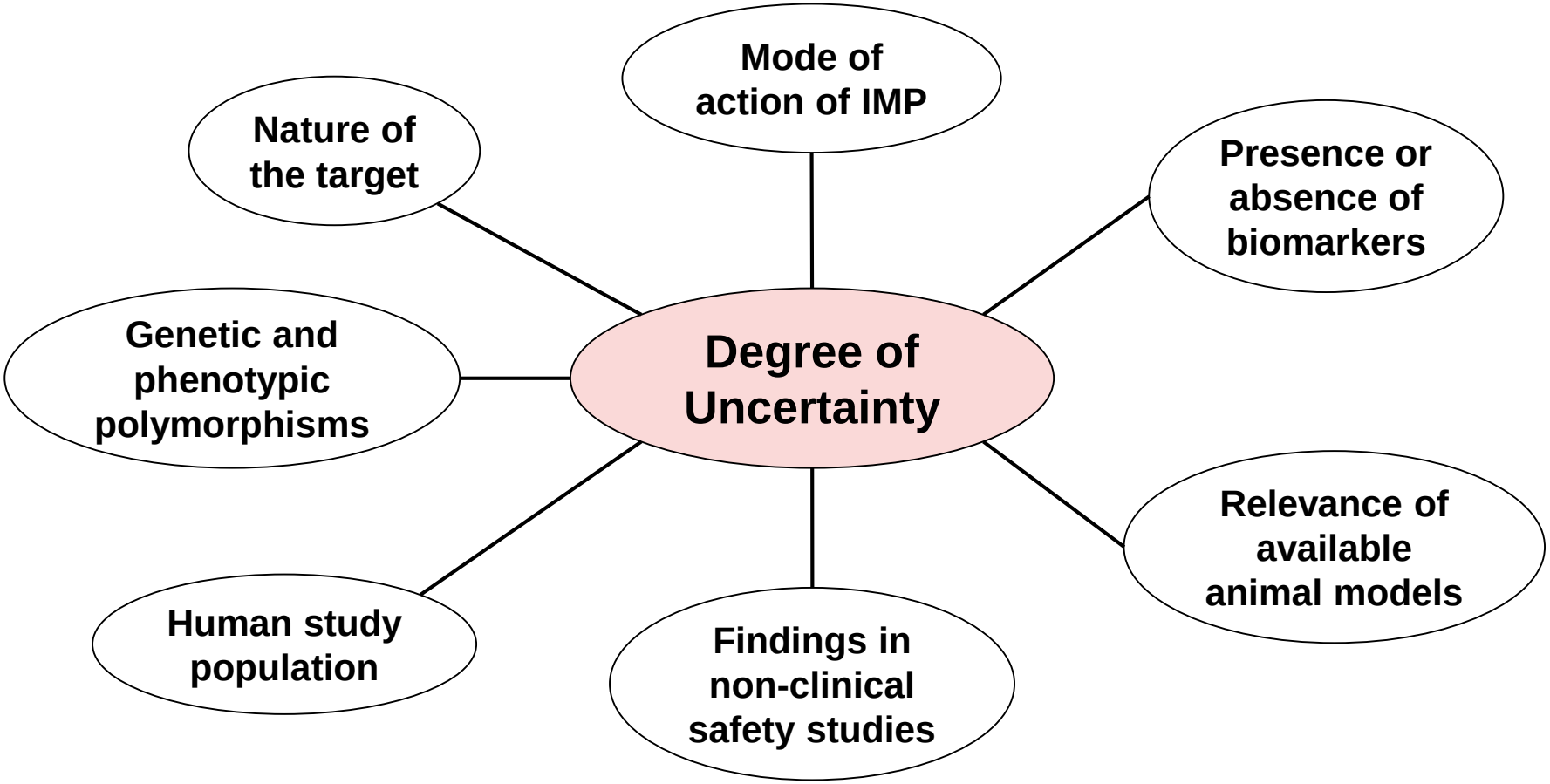
Special challenge for a first-in-human trial



Ultimate challenge: predicting the possible benefits and risks of an IMP in humans

From: EMEA/CHMP/SWP/28367/07 Rev. 1; 20 July 2017

Risk minimization for a first-in-human trial

- Based on the degree of uncertainty, **risk mitigation strategies** include:
  - Ensuring adequate quality of the IMP
  - Conducting non-clinical testing in addition to standard studies:
    - Assessment of relevance of animal models, e.g. by human-derived material
  - Applying scientific rationale in the selection / definition of:
    - Starting dose, dose escalation, maximum expected exposure of IMP
  - Applying appropriate risk mitigating measures in the trial design and trial conduct

- Decision before and during the trial should be based on:
  - Rigorous interpretation of the totality of available data including new and emerging data

- Vast majority of first-in-human trials completed without adverse impact on participants
  - **3,100** first-in-human trials conducted in EU since 2005 (EudraCT)

- **BUT**: two tragic events in first-in-human trials: TGN1412 and BIA 10-2474

From: Ponzano S et al. Clin Pharmacol Ther 2017 Nov 6. doi: 10.1002/cpt.899
Bonini S et al. N Engl J Med 2016;375:1788-9

Serious adverse events in TGN1412 first-in-human trial

- **TGN1412:** first-in-class superagonistic humanized monoclonal antibody specific for the T cell co-stimulatory molecule CD28 intended for the treatment of autoimmune diseases

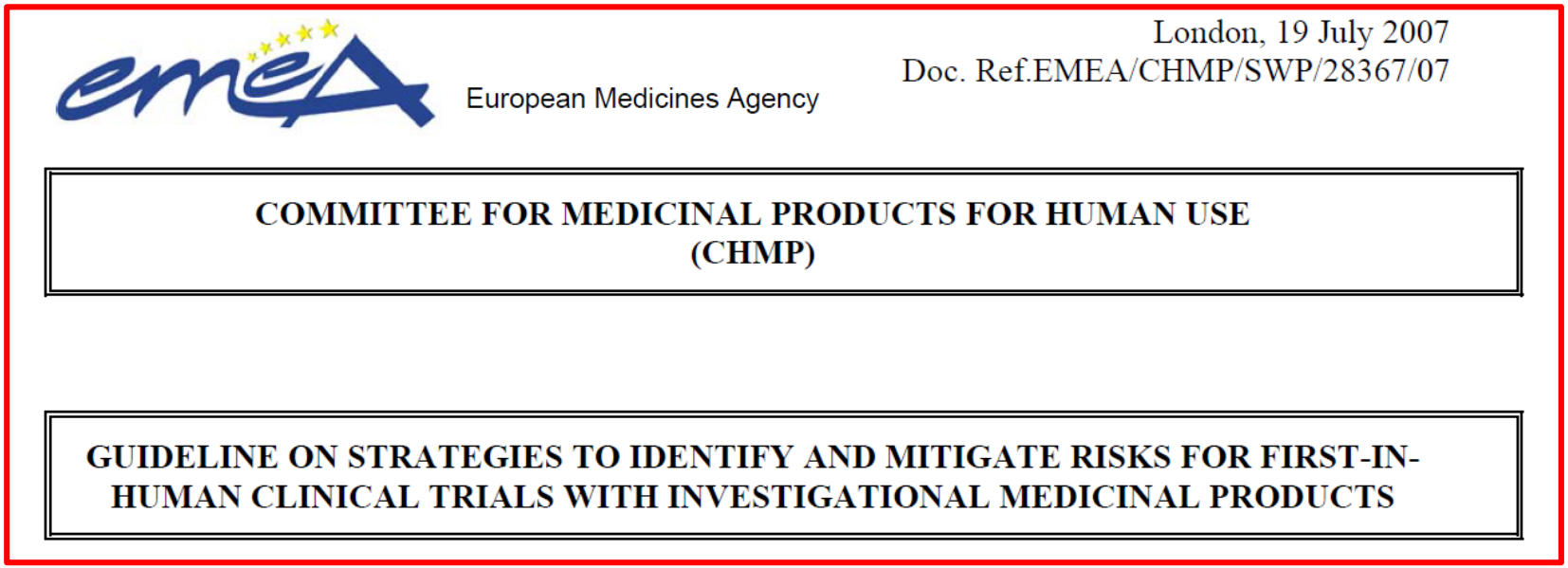
- **London, March 13, 2006:** first administration of TGN1412 (0.1 mg/kg) to 6 healthy men:
  - Within 90 min after infusion in all subjects: systemic inflammatory response
    - rapid induction of multiple proinflammatory cytokines (“cytokine storm”)
    - headache, myalgias, nausea, diarrhea, erythema, vasodilatation, hypotension
  - Within 12 – 16 hrs: all subjects critically ill requiring transfer to ICU
    - pulmonary infiltrates, lung injury, renal failure, disseminated intravascular coagulation
  - Prolonged cardiovascular shock and acute respiratory distress syndrome in two subjects
  - All 6 subjects survived but with patches of necrosis on fingers and toes in one subject

- **Non-clinical data:** high homology of CD28 receptor in human and cynomolgus monkey
  - Specificity of regulatory T cell activation by TGN1412 assumed based on study results
  - Starting dose determined based on data from rodents, primates and human cells

From: Kenter JH et al. Br J Clin Pharmacol 2015;79:545-7
Hünig T. Nat Rev Immunol 2012;12:317-8
Suntharalingam G et al. N Engl J Med 2006;355:1018-28

Consequences of the TGN1412 first-in-human trial

- **Investigation of potential causes** by expert scientific groups:
  - Starting dose sufficient for 90% CD28 receptor occupancy in human body
  - Species differences in CD28 expression on CD4+ effector memory T-cells: macaque cells but not human cells lose CD28 expression during cell differentiation
  - Failure of human PBMC assay: lack of cellular contacts => starting dose 200-fold lower



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

- **Introduction** of new non-clinical and clinical concepts for risk minimization, e.g.
  - Starting dose based on minimum anticipated biological effect level (MABEL)

From: Kenter JH et al. Br J Clin Pharmacol 2015;79:545-7
Hünig T. Nat Rev Immunol 2012;12:317-8

Serious adverse events in BIA 10-2474 first-in-human trial

- **BIA 10-2474:** non-first-in-class reversible fatty acid amide hydrolase (FAAH) inhibitor intended for the treatment of medical conditions in which there is an advantage in enhancing the levels of endocannabinoids, e.g. neuropathic pain

- **Trial design:** integrated SAD (8 dose cohorts) – MAD (5 dose cohorts) trial with > 2-fold dose increase in final cohorts (SAD: 40 mg => 100mg; MAD: 20 mg => 50 mg)

- **Rennes, January 10, 2016:** fifth administration of BIA 10-2474 (50 mg) to 6 healthy men in final MAD dose cohort; sixth administration to 5 subjects on January 11
  - Neurologic adverse events (headache, ataxia) in one subject requiring hospitalization
    - condition deteriorated on the next day: unconsciousness, mechanical ventilation
    - progress to **brain death** on the following day
  - Similar neurologic adverse events in 4 further subjects requiring hospitalization
    - headache, cerebellar syndrome, memory impairment, altered consciousness
    - subsequent improvement with residual memory impairment
  - MRI findings: bilateral and symmetric cerebral lesions, including microhemorrhages

From: Kerbrat A et al. N Engl J Med 2016;374:1717-25
Eddleston M et al. Br J Clin Pharmacol 2016;81:582-6

Consequences of the BIA 10-2474 first-in-human trial

- **Investigation of potential causes** by specialist committee (TSSC) and scientific groups:
  - Compound toxicity via off-target effects on brain cell structures (low target specificity)
  - Multiple doses higher than needed for complete and lasting FAAH inhibition
  - Specific pharmacokinetic features leading to gradual brain accumulation

- **Revision** of the FIH guideline by the EMA including significant changes, e.g.
  - Enlarging the scope to early clinical trials and integrated protocols


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/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

From: Ponzano S et al. Clin Pharmacol Ther 2017 Nov 6. doi: 10.1002/cpt.899
van Esbroeck et al. Science 2017:356;1084-7
TSSC report, 18 April 2016

Summary: What is so special about a first-in-human trial?

Points to consider

- Early clinical development of an IMP has an intrinsic element of uncertainty in relation to the possible benefits and risks of the IMP.
- Uncertainties in the translation of non-clinical data impact the predictability of risks associated with the first administration of an IMP to humans.
- Innovative and diligent risk mitigation strategies will further enhance the safety of subjects during the conduct of a first-in-human trial.

Actions

- For a first-in-human trial, potential risks are to be identified and appropriate risk mitigation strategies to be applied based on the degree of uncertainty.
- These strategies refer to IMP quality, non-clinical studies, dosing selection, and planning and conduct of the first-in-human trial.
- Safety and well-being of trial subjects should always be the priority.

GRÜNENTHAL