Is a Maximal Tolerated Dose in Human useful for drug development?

How to define an acceptable highest dose to be tested?

EuFeMED, London

Pre-conference Workshop

17-May-2017

Eric Legangneux

Philippe Grosjean

Background

- **Current guidelines ICH / EMA**
  - EMA (September 2007) : Guideline on strategies to identify and mitigate risks for First in Human
  - ICH (June 2009) : Guidance on non clinical safety studies for the conduct of Human clinical trials and marketing authorization for pharmaceuticals. M3(R2)
- **Draft Guidance EMA / calendar**
  - EMA (November 2016) : Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	<DD Month YYYY>
Date of coming into effect	<DD Month YYYY>

Papers about MTD

- **Pr A. Cohen , 2007**

DOI:10.1111/j.1365-2125.2007.03023.x

British Journal of Clinical Pharmacology

Editors' view

Should we tolerate tolerability as an objective in early drug development?

A. Cohen, European Editor, British Journal of Clinical Pharmacology
Centre for Human Drug Research, Zernikedreef 10, 2333CL Leiden, The Netherlands

- **Club Phase I meeting (Paris) :** March 20th, 2008
  - MTD and Top dose (Dr Michel Sibille)
  - http://www.clubphase1.com/3-0-EVENEMENTS+.html
- **Recent accidents**
  - Te Genero (2006) , Bial 10-2474 (2016)

Papers about MTD

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 582–586 582

EDITORIAL

Implications of the BIA-102474-101 study for review of first-into-human clinical trials

Correspondence M Eddleston, PTT, QMRI E3.21, 47 Little France Crescent, Edinburgh EH9 2BS, UK. E-mail: m.eddleston@ed.ac.uk

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Michael Eddleston[1,2], Adam F. Cohen[3] and David J. Webb[1]

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Acute Neurologic Disorder from an Inhibitor of Fatty Acid Amide Hydrolase

Anne Kerbrat, M.D., Jean-Christophe Ferré, M.D., Ph.D., Pierre Fillatre, M.D., Thomas Ronzière, M.D., Stéphane Vannier, M.D., Béatrice Carsin-Nicol, M.D., Sylvain Lavoué, M.D., Marc Vérin, M.D., Ph.D., Jean-Yves Gauvrit, M.D., Ph.D., Yves Le Tulzo, M.D., Ph.D., and Gilles Edan, M.D., Ph.D.

The MTD concept in human

- **Assumption with the MTD investigation**
  - Defining a MTD supposes reaching first a Non TD
  - Are AE always dose proportional ?
  - Off target effects from preclinical studies with appropriate monitoring
    - Human specific AE
  - Exaggerated pharmacology
- **What is the interest of the knowlege of the MTD in drug development**
  - Interest of a safety margin
    - Definition (x 5, x10), covering real life world, outliers, phenotypes , DDI)
    - At which dose shall the safety margin be applied
  - Other impact on drug development ?
- **MTD in human : a toxicological end point ?**
  - Not anymore acceptable (ethical concern ?, usefulness?)
  - End point in human should be more clinically driven

MTD in the draft guidance

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

- **Lines 424 - 425**
  - "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified."
- **Lines 429 -433**
  - "For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should be clearly defined and not be exceeded once it has been determined. The potential therapeutic or clinically relevant dose (exposure) and the expected benefit/risk balance should always be considered when defining the dose range. A trial design using a MTD approach is considered to be unethical for healthy volunteers.."

New paradigm

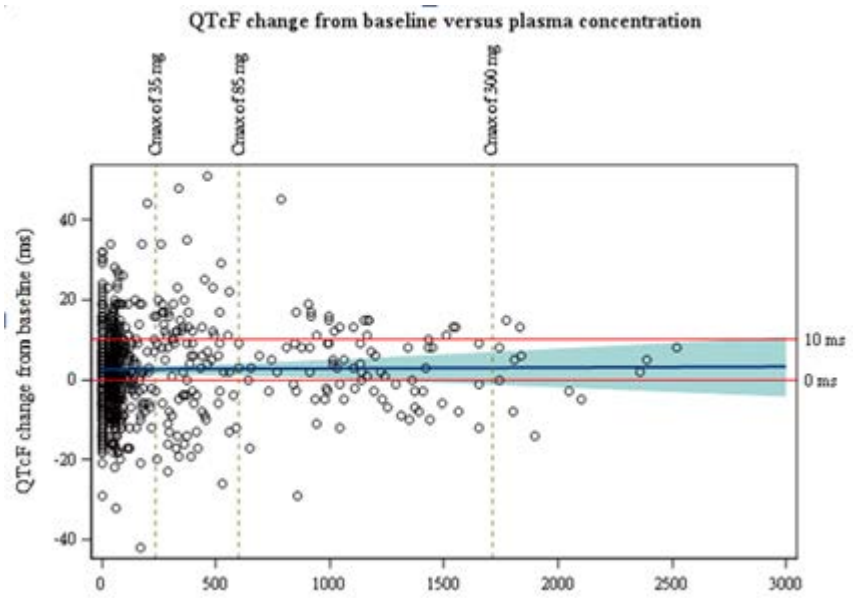
- **If the MTD is not anymore the objective or the limiting factor**
  - Need to enrich the FIM with more PD markers
    - If possible
    - Absence should be justified
  - Taken into account in the dose escalation decision process ?
  - Need of a safety margin
    - Outliers, DDI, real life (ref to TQTc studies)

- **Ethical versus usefulness**
  - Wording for a guideline
  - Ethical in patients (?)

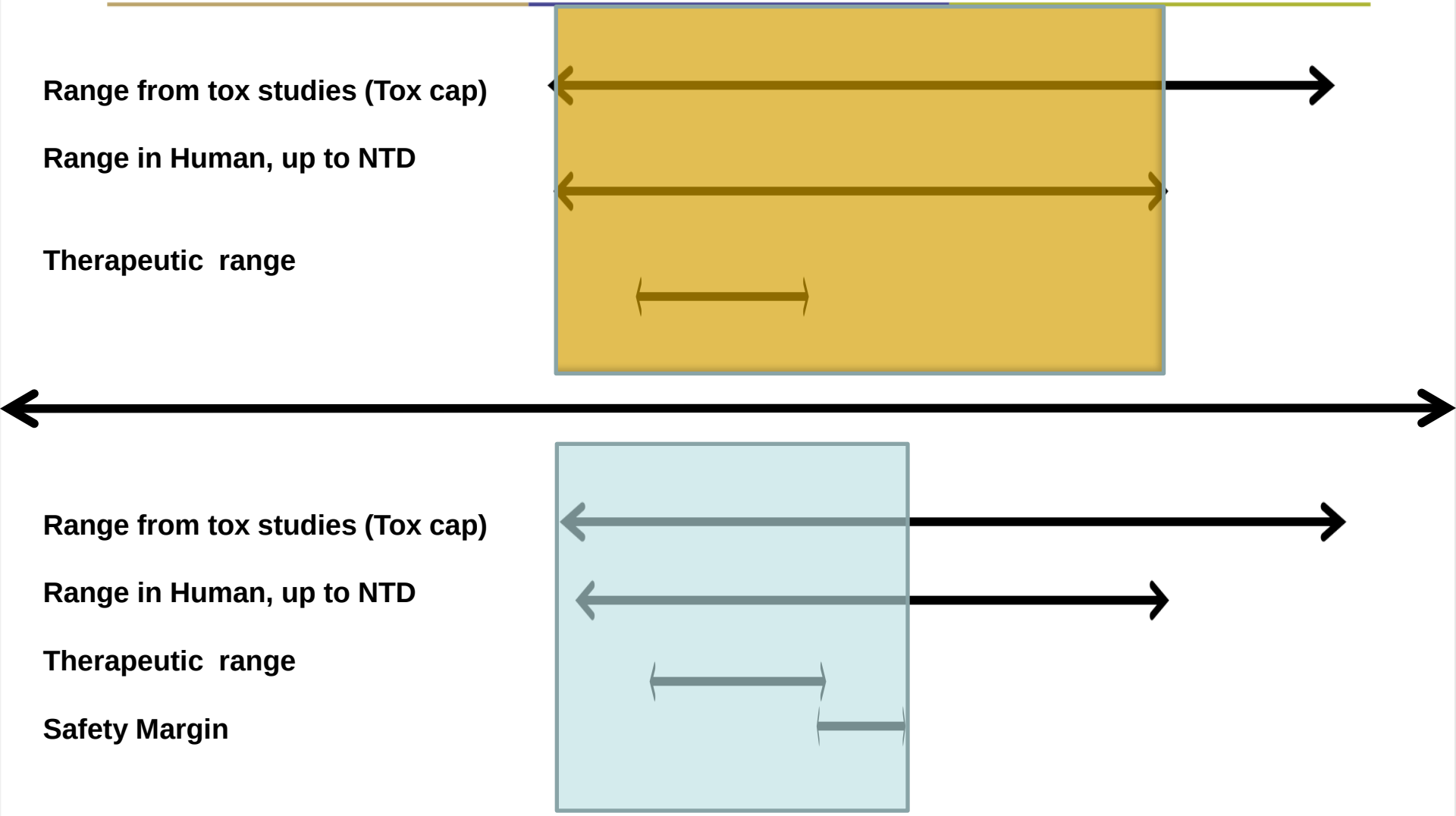
- **Concept of « Maximal Investigated Dose »**
  - Should be scientifically justified.
    - Upper range estimate of the therapeutic dose + safety margin

When is the knowledge of the MTD useful ?

- Define the human PK/PD relationship.
  - Identification of the E_{max} is required for optimal dose selection in patients.
  - Drugs with low safety margin
- Conc / effect of the potential QTc prolongation
- Information about poisoning,
  - number of pills per box
- Drug concentration in the target organ is lower than in plasma
- Dose regimen.
  Higher dose might be needed for longer duration



New paradigm- Range of investigation



Questions

- **Limitation to therapeutic dose range**
  - Therapeutic dose range unknown
  - Estimate based on animal model(s)
  - Need of a safety margin
    - Outliers, DDI, real life (ref to TQTc studies)

- **Ethical versus usefulness**
  - Wording for a guideline
  - Ethical in patients (?)

- **Concept of « Maximal Investigated Dose »**
  - Should be scientifically justified.
    - Upper range of the therapeutic dose estimate + safety margin
    - Apply sTTC

Questions

- **Early input of the « Therapeutic dose range » investigation**
  - Could impact the classical Phase IIa « Dose finding »
  - Could make the FIM package (combined studies) more complex
  - Early involvement of patients
  - FIM and PoC interleaved
  - FIM studies paused and re-open a longer time

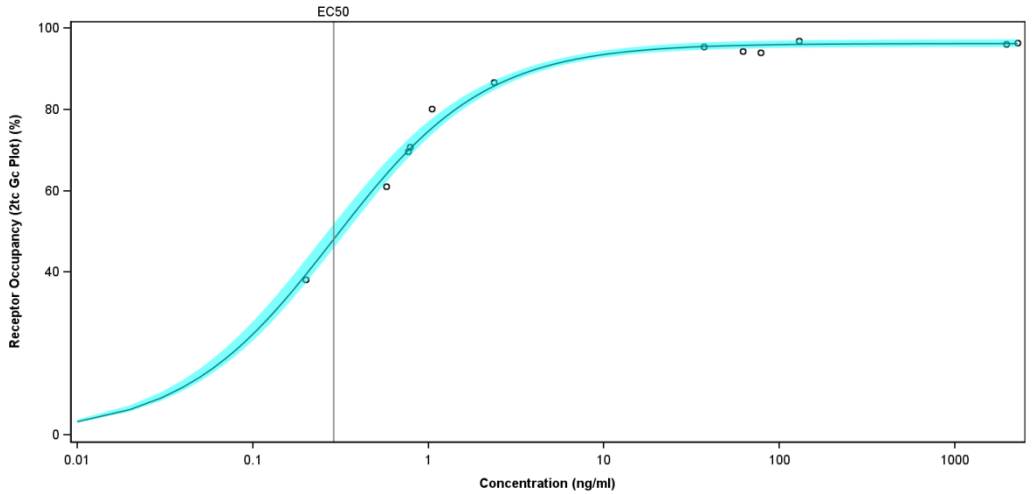
- **With what can the new FIM studies be enriched**
  - Biomarkers
  - Preclinical data

Example #1

- **FIM investigation of ABC123**
  - SAD : 0.3, 1, 3 10 30, 100, 300 and 800mg
    - Well tolerated, AE in relation with the MoA of the compound leading to define 800mg as NTD. Then MTD = 300 mg
  - MAD : 10, 30, 100, then 50 mg. MTD = 50 mg

- **PET scan study**
  - **Plasma concentration of ABC1232 versus receptor occupancy in the brain (EC50)**

- **Conclusion**
  - 90% RO corresponds to 3 to 5 mg.

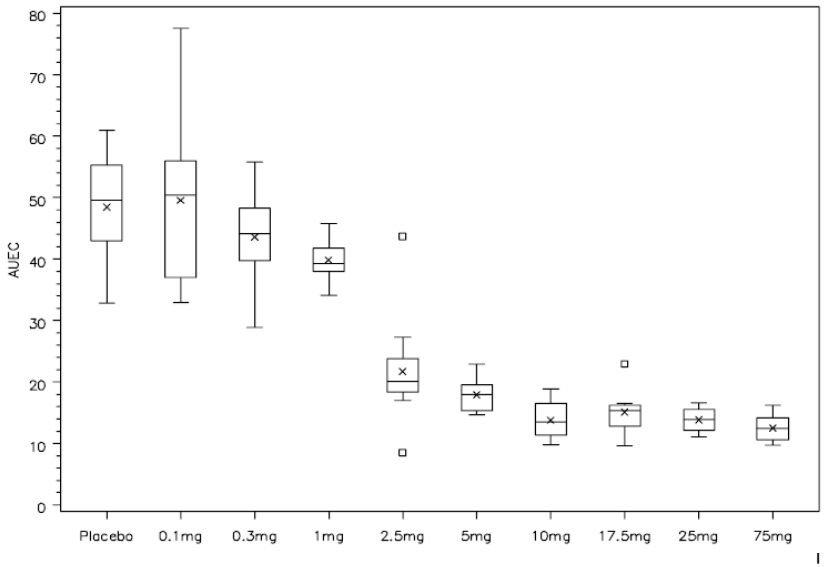


Example #2

- **FIM investigation of XYZ123**
  - SAD : 0.1, 0.3, 1, 2,5, 5, 10, 17.5, 25, 75mg
    - Well tolerated, AE : bradycardia leading to define 75mg as NTD. Then MTD = 25 mg
  - MAD : 0.3, 1, 2.5, 10, 20mg. No MTD
- **Biomarker : Lymphocyte count (MoA of the compound)**
  - **Plasma concentration of XYZ123 versus lymphocyte count**
- **Conclusion**
  - Therapeutic efficacy foreseen with 80% reduction of the LC
  - Therapeutic dose is 2mg

Figure 11-1 **Lymphocyte AUEC$_{(0-24)}$ by dose group-Safety population**

Part I: Fasted



Example #3

- **FIM investigation of A0001**
  - NOAEL 0.3 mg/kg (dog), 1 mg/kg (rat)
    - Exposure: Cmax≈300 ng/mL AUC≈4500 ng.h/mL both species
  - SAD : 1, 2, 6, 12, 24 and 48 mg
    - Peak plasma drug concentrations higher than predicted from dog data (Protocol amended to allow higher peak plasma concentrations)
    - Well tolerated, dose escalation based an a maximum target PD parameter
    - Exposure at 48 mg: Cmax≈450 ng/mL AUC≈33 000 ng.h/mL
  - MAD : on going
- **Biomarker : LVEF**
  - PD activity less than anticipated based on PK/PD relationship in dog model
  - Target PD effect detected at 24 and 48 mg
- **Discussion**
  - Limits of animal data (toxicity, PK, PKPD model…)
  - FIH top dose vs NOAEL
  - Therapeutic index