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

The views and opinions presented here represent those of the speakers and should not be considered to represent the Club Phase I or the speaker’s companies.
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- **Draft Guidance EMA / calendar**

<table>
<thead>
<tr>
<th>Adopted by CHMP for release for consultation</th>
<th>10 November 2016</th>
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<tr>
<td>Start of public consultation</td>
<td>15 November 2016</td>
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<td>End of consultation (deadline for comments)</td>
<td>28 February 2017</td>
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<td>Adopted by CHMP</td>
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Papers about MTD

- Pr A. Cohen, 2007

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](http://www.clubphase1.com/3-0-EVENEMENTS+.html)

- **Recent accidents**
  - Te Genero (2006), Bial 10-2474 (2016)
Papers about MTD

EDITORIAL

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

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Received 22 February 2016; accepted 22 February 2016

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The NEW ENGLAND JOURNAL of MEDICINE

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 knowledge 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 $E_{\text{max}}$ 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

Range from tox studies (Tox cap)
Range in Human, up to NTD
Therapeutic range

Range from tox studies (Tox cap)
Range in Human, up to NTD
Therapeutic range
Safety Margin
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 ABC123 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](image)
**Example #3**

- **FIM investigation of A0001**
  - NOAEL 0.3 mg/kg (dog), 1 mg/kg (rat)
    - Exposure: Cmax$\approx$300 ng/mL, AUC$\approx$4500 ng.h/mL both species
  - SAD: 1, 2, 6, 12, 24 and 48 mg
    - Peak plasma drug concentrations higher than predicted from dog data
      (Protocol amended to allow higher peak plasma concentrations)
    - Well tolerated, dose escalation based on a maximum target PD parameter
    - Exposure at 48 mg: Cmax$\approx$450 ng/mL, AUC$\approx$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