# EMA GUIDANCE FOR FIH STUDIES

A Brief Overview and Comment


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# SLIDE WITH SAMPLE AGENDA



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# HISTORY



| | | |
|---|---|---|
| March 2006 | TeGenero trial | Severe inflammatory reactions to TGN1412, including catastrophic systemic organ failures. |
| March 2007 | RSS Working Party | Report on Statistical Issues in First-in-Man studies |
| July 2007 | EMA Guideline adopted | Guideline on Strategies to Identify and Mitigate Risks for First-inhuman Clinical Trials with Investigational Medicinal Products |
| January 2016 | BIAL trial | Fatality and several serious adverse events in trial of BIA 10-2474 |
| July 2016 | EMA Concept Paper | Concept paper on the revision of the 2007 guideline |
| November 2016 | EMA Draft Guideline | Revised guideline released for consultation |

# GUIDELINE CONTENT



## The Current Guideline:

- Focuses on non-clinical aspects of drug development
- Only considers SAD studies
- For clinical development, more of a points to consider document

## The Revised Guideline (draft):

- Gives considerably more information on the design of FiH studies
- Explicitly covers the “umbrella-protocol” practice, including considerations for moving from SAD to MAD parts
- More concrete guidance on choice of starting dose
- Calls for maximum dose / dose range / exposure margin to be defined in the protocol

# GUIDELINE CONTENT



**Structure of the Revised Guideline (draft):**

- General Considerations
  - Mode of action, nature of target
- Quality Aspects
- Non-clinical Aspects
  - Relevance of animal model (incl. species), PD, PK, safety pharmacology, toxicology
- Dosing Selection for FiH and Early Clinical Trials
  - General aspects, starting dose, dose escalation, maximum dose, moving from single to multiple dosing, route of administration, patients
- Planning and Conduct of FiH and Early Clinical Trials
  - General aspects, overall design, integrated protocols, choice of subjects, assessments and interventions, considerations for all cohorts, precautions within a cohort / between cohorts / between study parts, dose escalation scheme, stopping rules. Monitoring / communication of AEs, documentation
  - Sponsor / investigator responsibilities, site facilities & personnel

# GUIDELINE CONTENT



## Estimation of Starting Dose

- Use NOAEL (no observed adverse effect level) from non-clinical safety study, estimate equivalent human exposure using state of the art modeling or allometric scaling
- Also determine MABEL (minimal anticipated biological effect level), PAD (pharmacologically active dose), ATD (anticipated therapeutic dose range) from non-clinical pharmacology studies (including ex-vivo and in-vitro)
- Apply safety factor – justify in IB and protocol
- Starting dose should be below anticipated active dose levels

# GUIDELINE CONTENT



## Dose Escalation

- Dose increases should be outlined in the protocol
- Dose increases should be guided by dose/exposure-toxicity or dose/exposure-effect relationship
- If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust planned dose levels
- Any dose skipping should take aspects such as steepness of dose-response curve or saturation of target into account and requires a substantial amendment.

## Maximum Dose and Dose Range

- Maximum dose or exposure should be pre-defined and justified in the protocol
- This should not be exceeded without approval of a substantial amendment
- Justification should be based on all available non-clinical and clinical data
- If it is not possible to predefine definite doses in all study parts, include clear dose selection criteria
- If no absolute maximum dose, then justify the maximum fold increase in dose, and maximum exposure limit

# GUIDELINE CONTENT



## Integrated Protocols

- Analyze and integrate data from previous parts before proceeding to next part
- Pre-specify all parts, including potential modifications
- Overlap of SAD and MAD may be acceptable if supported by decision tree and review of all available data
- Other multiple dose parts (food effect, DDI) should not overlap with SAD/MAD

# GUIDELINE CONTENT



## Precautions to apply between treating subjects within a cohort

- Sentinel dosing is considered appropriate for all cohorts
- Adequate observation period between sentinel and remaining subjects
- After observation period, review all data before allowing dosing of further subjects

## Precautions to apply between cohorts

- Proceed to next cohort after previous cohort is complete
- All relevant data (PK, AEs) from cohort “n” should be reviewed prior to allowing dosing of cohort “n+1”.

## Stopping Rules

- Protocol should define rules to stop dosing, permanently or temporarily, individual, cohort, escalation, progression to next part, etc.
- Required stopping criterion based on clinical exposure ($C_{max}$ or AUC) equivalent to exposure at NOAEL in the most sensitive non-clinical species (adjusted by safety factors).

# SOME GENERAL COMMENTS



**Toxicology**

- Relevance of animal species based on target similarity to humans:
  - Primary pharmacology versus off-target effects

**Substantial Amendments in FiH Trials**

- Required to adjust predefined dosing selection
  - Predefining doses is usually difficult, flexibility is required
  - Define dose selection criteria rather than doses
  - Otherwise amendments needed after each dose level?

**Maximum Dose / Dose Range**

- Exposure to be limited by NOAEL
  - This may restrict studied doses to ineffective dose range
  - Results in little / no information at supratherapeutic doses

# SOME STATISTICAL COMMENTS



**General Considerations**

- "The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort"
  - Do we require a statistical justification of the sample size before each cohort??

**Sentinel Dosing**

- Decision to proceed is based on n=1, with low sensitivity/specificity
  - Use risk-based approach

# OPPORTUNITIES FOR STATISTICS?



## Use of Modelling

- Frequent mention of modelling (PK/PD, PBPK) throughout several sections
  - “A state-of-the-art PK/PD modelling approach is recommended”
  - “[…] all relevant data should be integrated in a suitable modelling approach for the determination of the MABEL, PAD and/or ATD”
  - “The methods […] including methods for modelling […] should be included in the IB and summarised in the protocol”
  - “If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, […]”
  - “The review [of data between cohorts] should include comparison […] to any initial or updated PK and/or PD modelling and simulation.”

# OPPORTUNITIES FOR STATISTICS?



**Bayesian Methods for Dose Escalation (Whitehead et al, 2001):**

- Assumes cross-over design for SAD studies
- Based on power model (log-log-scale)

$$y_{ij} \mid s_i, \theta_1, \theta_2, v \sim N\left(\theta_1 + \theta_2 \ell_{ij} + s_i, v^{-1}\right)$$

$$s_i \mid \theta_1, \theta_2, \omega_0 \sim N\left(0, \omega_0^{-1}\right)$$

$$\theta_k \mid \omega_k \sim N\left(m_k, \omega_k^{-1}\right), k = 1,2$$

$$\omega_0 \mid \alpha_0, \beta_0 \sim Gamma\left(\alpha_0, \beta_0\right)$$

$$v \sim Gamma\left(\alpha_1, \beta_1\right)$$

- Can be used to calculate probability of exceeding individual / mean cap at next dose level
- Separate results for each set of prior distributions

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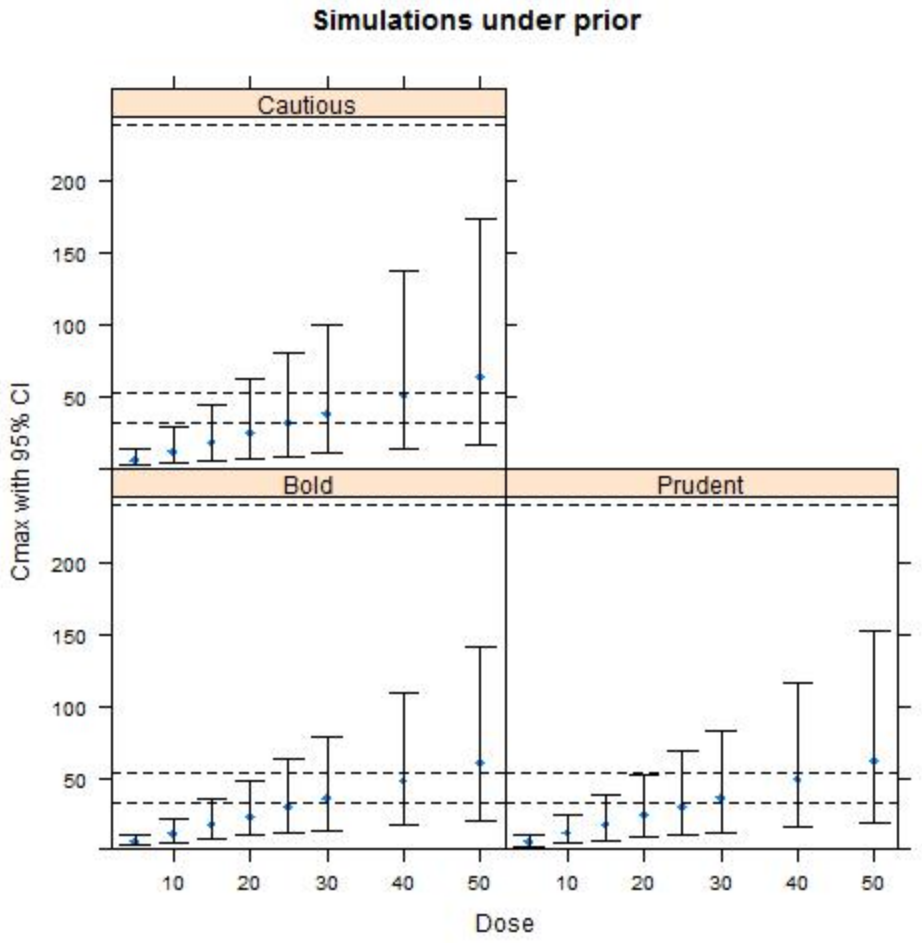
# OPPORTUNITIES FOR STATISTICS?





# CONCLUSIONS



- Draft revision of EMA Guideline on Strategies to Identify and Mitigate Risks for First-inhuman Clinical Trials with Investigational Medicinal Products is an improvement on the previous version.
- It introduces the idea of risk-based approaches to FiH trials.
- The guideline would have provided better protection for subjects in the TeGenero and BIAL trials.
- If implemented in its current form, there will be more of a burden on sponsors for FiH studies.
- Competent authorities will play a more active role in these studies.
- There are areas for statisticians and pharmacometricians to get involved in.

# REFERENCES

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