Centrale Commissie Mensgebonden Onderzoek

Participants in Phase I – a regulator's perspective: proof of pharmacology

non-standard!

Prof. Joop van Gerven, MD, PhD
neurologist-clinical pharmacologist
Chairman Central Committee on Research Involving Human Subjects CCMO

Overview

‘Non-Standard’ Hybrid Regulatory Role of CCMO: Part I and Part II but not MA

- governmental body responsible for all research in humans in The Netherlands
- central ethics committee
- Dutch competent authority for clinical trials under European Regulations

Regulatory Guidelines for Phase I

- first-in-man guidelines: focus on pharmacology
- overview of other relevant (preclinical) guidelines

Objectives of Phase I: proof of pharmacology

- ‘tolerability and safety’ (??)
- pharmacokinetics
- pharmacodynamics
- relevant (patho)physiology

} subject selection criteria

Regular European Trial Authorisations

European Competent Drug/Trial Authority + Independent Ethics Review Boards

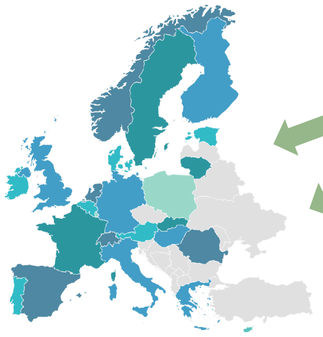
Drug Registrations

Trial Registrations
(including CTR, MDR, IVDR)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Part I
(Competent Authority)

Part II
(Ethics Committees)



Central Committee on Research Involving Human Subjects

Dutch Competent Trial Authority ⇔ Central Ethics Committee

Drug Registrations

CBG MEB

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Trial Registrations
(including CTR, MDR, IVDR)

ccmo

Part I
(Competent Authority)

Part II
(Ethics Committee)

One committee meeting

Integrated Scientific/
Regulatory/Ethics Approval

CCMO supervises 11 accredited Ethics Committees for trial evaluations

ccmo

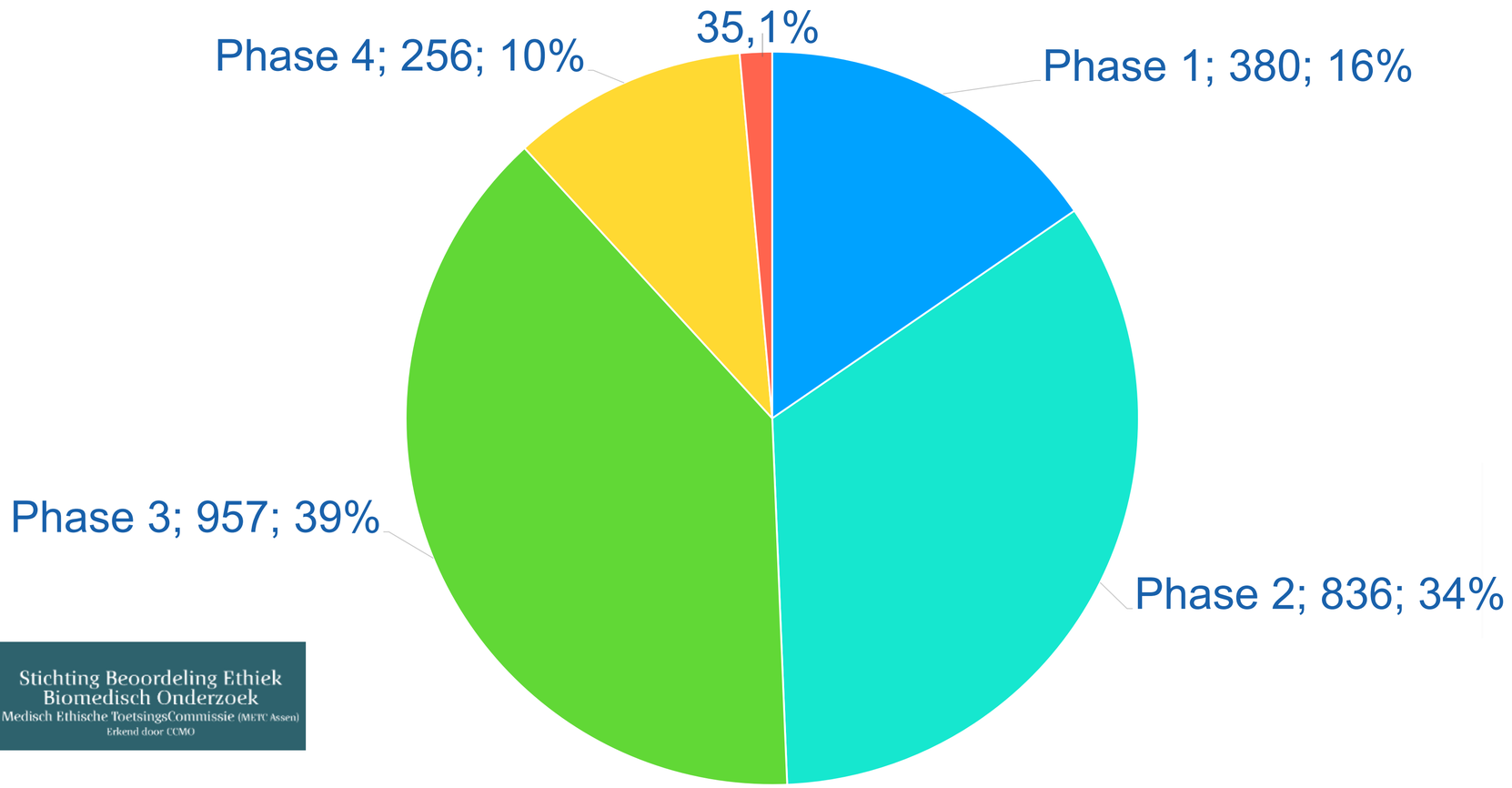
‘Non-Standard’ Regulatory Authority: Disciplines within Committee

- Physicians
- Pediatricians
- Jurists (*health law*)
- Methodologists
- Ethicists (*research ethics*)
- Lay members
- Medical Device and *In Vitro* Diagnostics Experts
- Hospital Pharmacists (*pharm.quality*)
- Clinical Pharmacologists (*incl.preclinical*)
- Behavioral Scientists
- Nursing Scientists
- Fundamental (Biomedical) Scientists
- Embryologists

CCMO-Office: regulatory and scientific support, Europe, administrative, legal and IT-support (CTIS)

Netherlands has Relatively Strong Phase I/II Position

Dutch Trials by Phase (2018-2022)



*Includes government / cooperative group / miscellaneous / OTC / not for profit collaborations

Guidelines related to Clinical and Non-Clinical topics relevant for the Evaluation of Phase I Studies

- **EMA FIH guideline** Strategies to identify and mitigate risks for **first-in-human and early clinical trials** with investigational medicinal products (2018)
- **FDA Guidance for industry** Estimating the **Maximum Safe Starting Dose** in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
- **ICH M3** (R2) **Non-clinical safety studies** for the conduct of human clinical trials for pharmaceuticals [CPMP/ICH/286/95]
- **ICH S7A** **Safety Pharmacology** studies for human pharmaceuticals
- **ICH S7B** Non-clinical evaluation of the potential for delayed ventricular repolarization (**QT interval prolongation**) by human pharmaceuticals
- **ICH S2** **Genotoxicity** testing [EMA/CHMP/ICH/126642/2008]
- **CTFG guidance on contraception** Recommendations related to **contraception and pregnancy testing** in clinical trials, version 1.1, date 21/09/2020
- **ICH S3B** Pharmacokinetics: repeated dose **tissue distribution** studies
- **RDT guideline** EMA guideline on **repeated dose toxicity** [CPMP/SWP/1042/99 Rev 1 Corr*]
- **ICH S3A** **Toxicokinetics**: the assessment of systemic exposure in toxicity studies [CPMP/ICH/384/95]
- **ICH M10** on **bioanalytical method validation** and study sample analysis
- **ICH M12** on **drug interaction studies** (draft)
- **EMA DDI guideline** Guideline on the investigation of **drug interactions** [CPMP/EWP/560/95]
- **EMA** Guidelines relevant for **advanced therapy medicinal products**
- **ICH S6 (R1)** Preclinical safety evaluation of **biotechnology-derived pharmaceuticals**
- **ICH S9** Non-clinical evaluation for **anticancer pharmaceuticals**
- **FDA Guidance for industry** Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of **Oncology Drugs and Biologics** Guidance for Industry
- **ICH S11** nonclinical safety testing in support of development of **paediatric pharmaceuticals**
- **Juvenile testing guideline** EMA guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for **paediatric indications** [EMA/CHMP/ICH/544278/1998]
- **Guideline local tolerance testing** Guideline on non-clinical **local tolerance** testing of medicinal products [EMA/CHMP/SWP/2145/2000 Rev. 1 Corr.]
- **M15** General Principles for **Model-Informed Drug Development**
- **ICH E6** **Good Clinical Practice**

Recommendation paper on principles of Good Laboratory Practices (GLP) for clinical trial applications under the EU Clinical Trials Regulation (Regulation (EU) No 536/2014)

Version 01

Document endorsed by GLP project team (experts from Clinical Trial Coordination Group, Nonclinical experts from EU member states & GLP inspectors from EU member states, EMA staff & EC DG GROW-GLP)	1 March 2024
Document endorsed by Clinical Trial Coordination Group	7 March 2024
Document endorsed by Nonclinical Working Party	13 March 2024
Document endorsed by EMA GLP inspectors Working Group	15 March 2024
Document endorsed by inspectors EU Working Group on GLP	6 March 2024

GLP-Certiticate Required for 'Pivotal Studies'!!!

First-in-Human Guidelines: EMA 2016-2018: Focus on Safety after BIA 10-2474 (January 2016)

- **EMA FIH guideline** Strategies to identify and mitigate risks for **first-in-human and early clinical trials** with investigational medicinal products (2018)

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

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	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) •• ••–••

EMA GUIDELINES SERIES

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

Joop van Gerven[1] and Milton Bonelli[2]

[1]*Central Committee on Research Involving Human Subjects CCMO, The Hague, The Netherlands and*
[2]*H&L Support Division, European Medicines Agency, London, UK Support Division, European Medicines Agency, London, UK*

Van Gerven JMA, Bonelli M. Commentary on the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1). *Br.J.Clin.Pharmacol* 2018;84(7):1401-1409

ccmo

First-in-Human Guidelines: Subject Selection

- **EMA FIH guideline** Strategies to identify and mitigate risks for **first-in-human and early clinical trials** with investigational medicinal products (2018)

Inclusion & Exclusion Criteria

🔍 **Risk-Adapted Participant Selection:**

- based on mechanism of action, PK/PD, target expression, and preclinical data
- systematic summary of preclinical data: IB-DeRisk

👤 **Healthy Volunteers vs. Patients**

- **Healthy volunteers**
  - IMP's with low/known risk, no therapeutic need
- **Patients**:
  - IMP's with higher or uncertain risk, disease-relevant PK/PD

🚫 **Exclude High-Risk Individuals**

- with comorbidities, interacting meds, or genetic vulnerabilities
- special populations (*eg* elderly, children) only if justified

🧬 **Tailored Criteria Based on IMP**

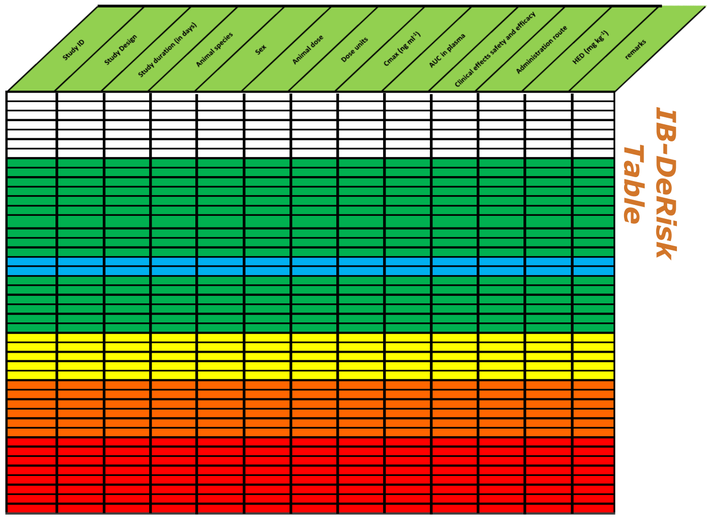
- consider target engagement, off-target effects, species differences

⏱️ **Staggered & Sentinel Dosing Recommended**

- dose 1 or 2 subjects first, monitor before full cohort

📄 **Protocol Justification Required**

- inclusion/exclusion criteria must support integrated risk strategy
- subject selection must agree with relevant study objectives



Van Gerven, J. & Cohen, A. Integrating data from the Investigational Medicinal Product Dossier/ investigator's brochure. A new tool for translational integration of preclinical effects. *Br.J.Clin. Pharmacol.* 84, 1457–1466 (2018).

First-in-Human Guidelines: Study Objectives

- **EMA FIH guideline** Strategies to identify and mitigate risks for **first-in-human and early clinical trials** with investigational medicinal products (2018)

Main Objectives

🛡️ **Prioritize Human Safety**

- assess **safety and tolerability**
- monitor adverse events, labs, ECGs, vital signs

- remember: **safety guideline** after BIA10-2475!
- but notice **first objective**: '**to study the human pharmacology**, tolerability and safety of the IMP and to compare how effects seen in **non-clinical studies translate into humans**'

📈 **Characterize Pharmacokinetics (PK)**

- understand **ADME**: absorption, distribution, metabolism, excretion
- define **dose-exposure relationship**

🎯 **Assess Pharmacodynamics (PD)**

- confirm **target engagement** and **mechanism of action**
- use **biomarkers** to guide dosing

📊 **Establish Dose-Escalation Pathway**

- identify **starting dose**, **MTD**, **PAD**, or **optimal biological dose**

🔄 **Enable Adaptive Trial Design**

- modify dose/cohorts based on **emerging safety/PK/PD data**
- apply **risk mitigation strategies** dynamically
- involve regulatory/ethics committee

➡️ **Inform Transition to Later Phases**

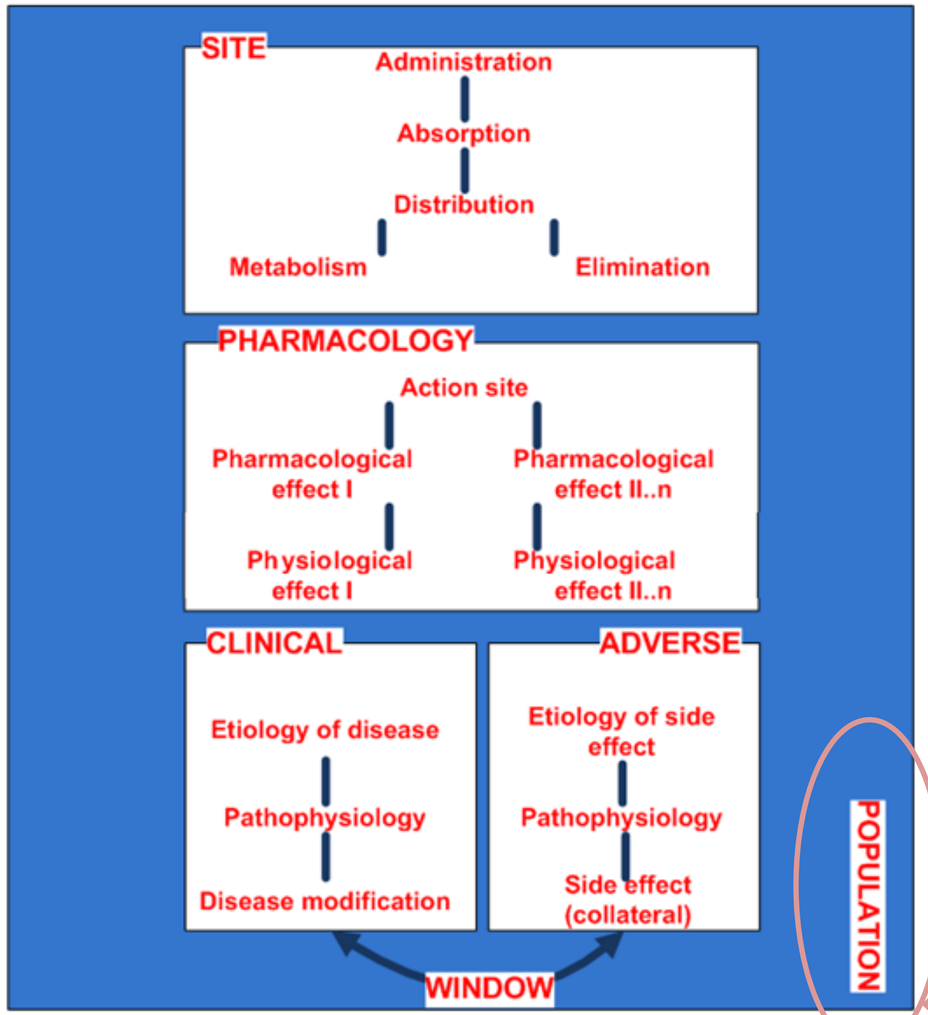
- generate data for Phase II dosing and **early efficacy** (if applicable/possible)
- **bridge design objectives** to patients in Phase II

in small groups,
human pharmacology
⇕
predictable tolerability/safety!

European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1), July 2017, Page 4/22

First-in-Human Guidelines: Study Objectives: Human Pharmacology and Translatability

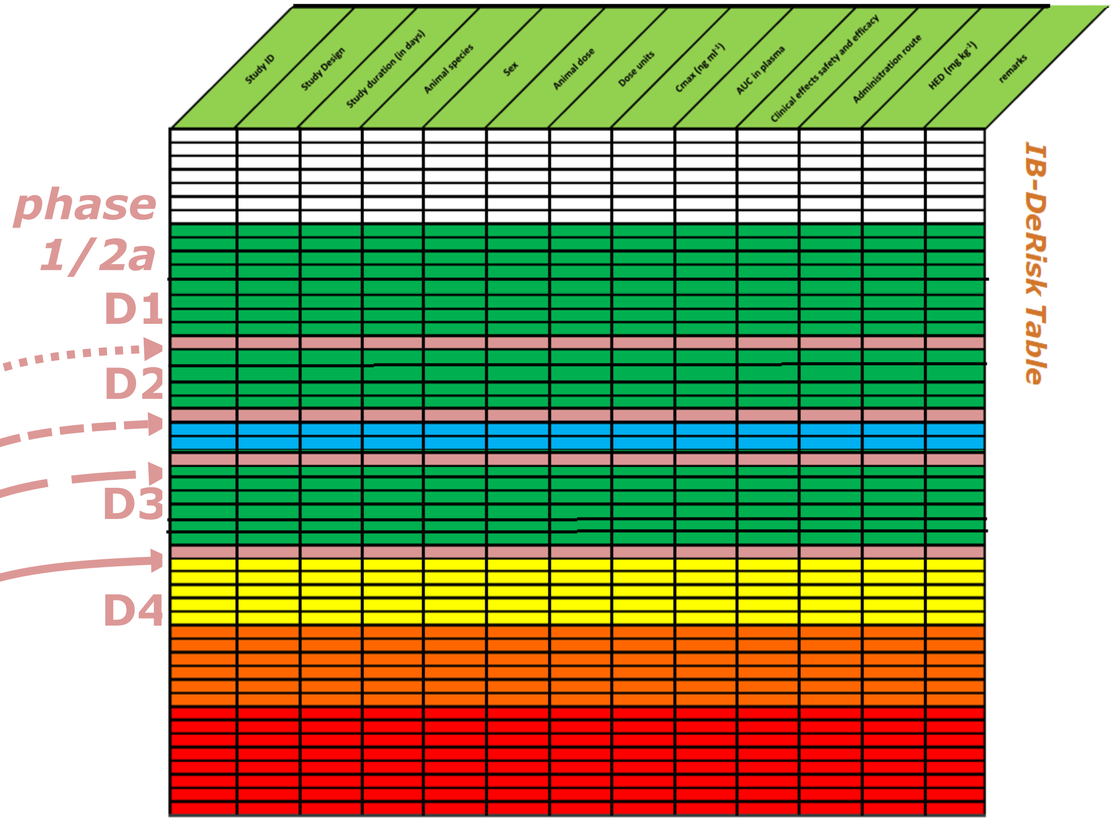
- **EMA FIH guideline** Strategies to identify and mitigate risks for **first-in-human and early clinical trials** with investigational medicinal products (2018)



Human Pharmacology

The purpose of FIH trials 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 and to compare how effects seen in non-clinical studies translate into humans.

European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1), July 2017, Page 4/22



Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? Nat Rev Drug Discov. 2010;9:856-65

Cohen AF, Burggraaf J, Gerven JM, Moerland M, Groeneveld GJ. The Use of Biomarkers in Human Pharmacology (Phase I) Studies. *Annu Rev Pharmacol Toxicol*. 2014 Oct 6.

van Gerven, J. & Cohen, A. Integrating data from the Investigational Medicinal Product Dossier/investigator's brochure. A new tool for translational integration of preclinical effects. *Br.J.Clin. Pharmacol.* 84, 1457–1466 (2018).

Conclusions

- **Phase I is – obviously – about safety and tolerability**
- **However, the first study objective is human pharmacology**
  - pharmacokinetics
  - pharmacodynamics
  - relevant physiological effects

  } also highly relevant for predictable safety!

- **Another objective is translation from animals to humans**
  - systematic predictions of human PK/PD-profile: MABEL, PAD, AHD
  - integrated assessment of preclinical information: *eg* IB-DeRisk
- **Study participants should be selected on integral objectives**

discussion

	patients	*healthy subjects*
‘higher risk compounds’	oncology, immunology	*ex vivo*, minimal dose
relevant PD	pathophysiology	challenge tests
tissue pharmacokinetics	pathological/surgical material	tissue sampling (skin, CSF)
pathophysiology	disease markers	relevant physiology