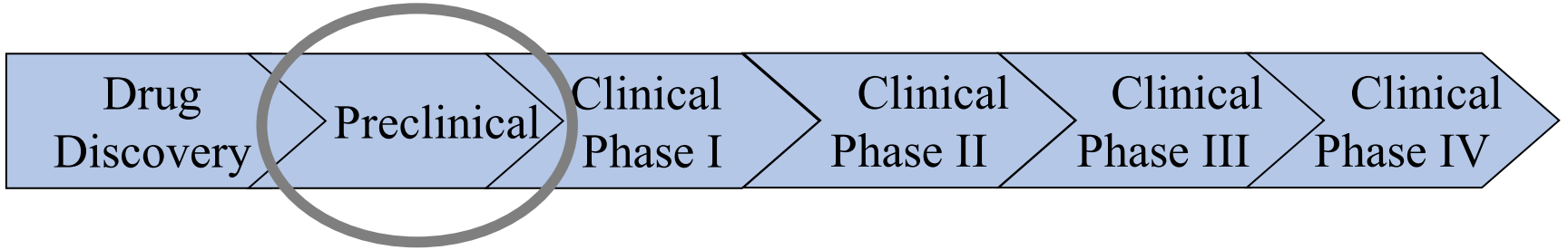
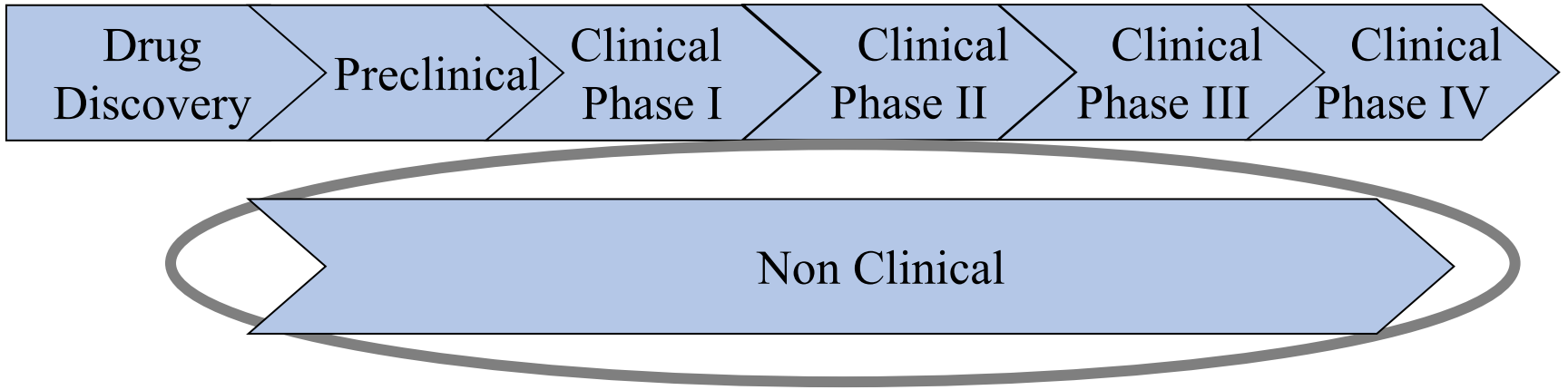
When?



→ **Preclinical safety package** prior to filing Clinical Trial Application (CTA) in Europe or Investigational new drug (IND) in USA for Phase I clinical trial



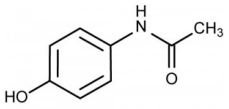
→ **Complete Nonclinical safety package** prior to **Biologic License or New Drug Application (BLA or NDA) OR Marketing Authorization Application (MAA) in Europe**

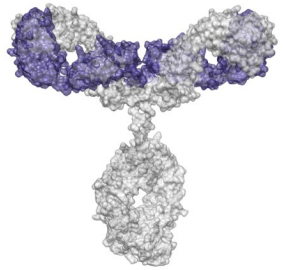
What ?

- Pharmacology studies (safety: CNS, cardiovascular and respiratory effects)
- General toxicity studies
- Toxicokinetic and nonclinical pharmacokinetic studies
- DART (Development and Reprotoxicity) studies
- Genotoxicity studies
- Carcinogenic potential (special cause for concern or intended for a long duration of use)
- Other nonclinical studies (case by case basis)

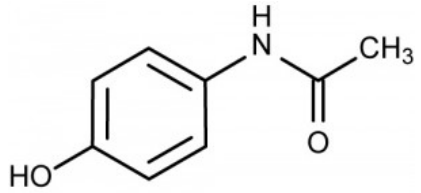
Key considerations

SME versus Biological

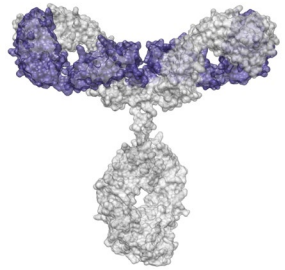




Chemical synthesis manufacture	Biomanufacturing
Organic chemical, Low MW	Protein, carbohydrate, DNA, virus, cell, very high MW
Metabolism (Cyt P450s, Phase 2 enzymes,…)	Catabolism (AA turnover…)
Highly distributed in the body	Poorly distributed in the body
Short half-life (hours)	Long half-life (days, weeks)
Therapeutic route: usually oral	Therapeutic route: usually IV, SC, IM,
Rarely species specific	Often species specific
Toxicity: “Off-target” effects (liver: main target organ)	Toxicity: “On-target” effects (exaggerated pharmacology)



- Pharmacology studies (safety) *in vitro & in vivo*
- General toxicity studies *2 species (rodent and non rodent) / Metabolism profile*
- Toxicokinetic and pharmacokinetic studies *Major metabolites*
- DART studies *2 species (rodent and non rodent)*
- Genotoxicity studies *The whole standard battery: in vitro & in vivo*
- Carcinogenic potential (special cause for concern or intended for a long duration of use) *2 rodent species*
- Other nonclinical studies (case by case basis) *e.g. Phototoxicity: in vitro & in vivo, immunotoxicity, Abuse liability studies,…*



- Pharmacology studies (safety) *in vivo only (not necessarily stand-alone studies)*
- General toxicity studies *Usually **1 Relevant #** species (NHP, max 6 months)*
- Toxicokinetic and pharmacokinetic studies *ADA assessment (immunogenicity)*
- DART studies *Usually 1 species (relevant ? homologous material ?)*
- Genotoxicity studies *Usually not (ADC with an organic linker)*
- Carcinogenic potential (special cause for concern or intended for a long duration of use)
- Other nonclinical studies (case by case basis) *e.g. Tissue Cross Reactivity, immunotoxicity,*

A **relevant species** is one in which the test material is **pharmacologically active** due to the **expression of the receptor or an epitope** (in the case of monoclonal antibodies) and which **shows similar tissue-cross reactivity profile to Human**: usually NHP (Non Human Primate), but if a second species is relevant, it should also be evaluated.

Current Regulatory Guidelines

Using preclinical data to determine appropriate FIH clinical doses Preclinical data & therapeutic window predictions

- **FDA Guidance for industry (2005):** Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In **Adult Healthy Volunteers**
- **EMA Guideline (R1, 2017):** Guideline On Strategies To Identify And Mitigate Risks For First-In-Human Clinical Trials With Investigational Medicinal Products
  - **HV and Patients**

- **ICH M3(R2, 2009):** Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
  - It also covers the estimation of the first dose in human for **Exploratory clinical trials and Microdose trials**
- **ICH S9 (2010):** Guideline on nonclinical evaluation for anticancer pharmaceuticals
  - **Patients with advanced cancer and limited therapeutic options**

Endpoints used for determination of the Maximum Recommended Starting Dose (MRSD)

Toxicity Endpoints

NOAEL

No Observed Adverse Effect Level

- Determined from the GLP Toxicology and Safety Pharmacology studies in animals
- Rodents and/or Non-Rodents: The most sensitive species (or most relevant if justified)

Oncology

Advanced cancer, Small molecules

STD10

Severely Toxic Dose in 10% of rodents

HNSTD

Highest Non-Severely Toxic Dose in non-Rodents

PD Endpoints

MABEL

Minimal Anticipated Biological Effect Level

- In vitro pharmacology (different species including human)
- Effective concentrations (EC20, EC50,..) from in vitro or in vivo data, measured or estimated RO
- PK/PD modeling data

PD Endpoints

PAD

Pharmcologically Active Dose

ATD

Anticipated therapeutic Dose

Single & Multiple Ascending Doses (SAD & MAD)

EMA guideline revision of 2017 introduced specific recommendations for combination and integrated protocol: **combined SAD/MAD**, **food Effect/drug-drug interaction**.

Dose selection and escalation should be reviewed based on all **emerging human PK and PD data** **from previous cohorts** and should not be considered fixed based on the original assessment of the non-clinical data

Decision for **progression from SAD to MAD** should be made **based on PK-PD modelling** where possible and **sentinel dosing** should be used for all cohorts**, both SAD and MAD**, unless otherwise justified.

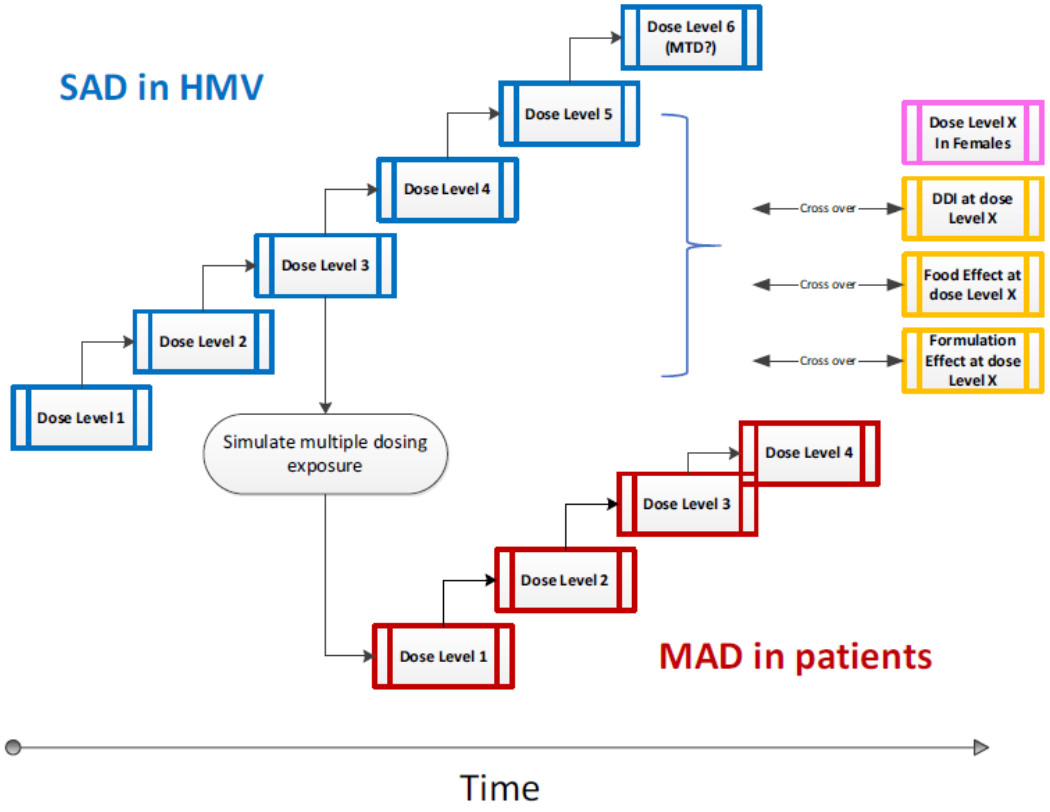
Sentinel dosing requires on day one of the study that one participant is randomised to active and one participant is randomised to placebo. Both subjects are then observed for a minimum of 24 hours before the remainder of the cohort is dosed.

MAD studies are intended **to fully characterize the pharmacokinetics of a drug** and its metabolites (NME) at **steady state**, investigate a drug's **accumulation** potential, explore its **dose proportionality**, and determine the Maximum Tolerated Dose (**MTD**).

Accelerate early clinical development

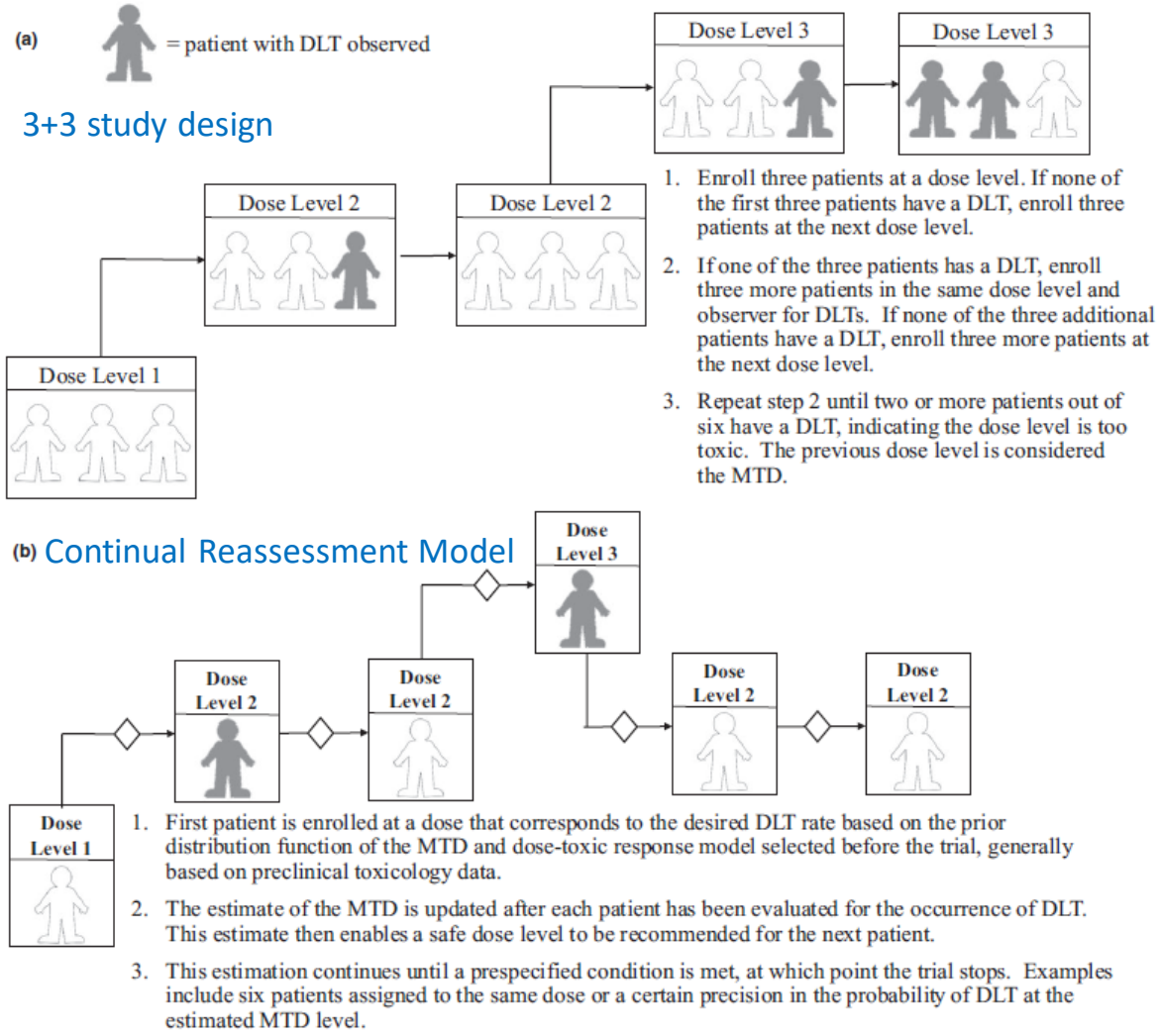
without compromising the safety and well-being of participants

Single & Multiple Ascending Doses (SAD & MAD)



Example study schema for a first-in-human trial with multiple objectives

Shen et al. Clin Transl Sci (2019)



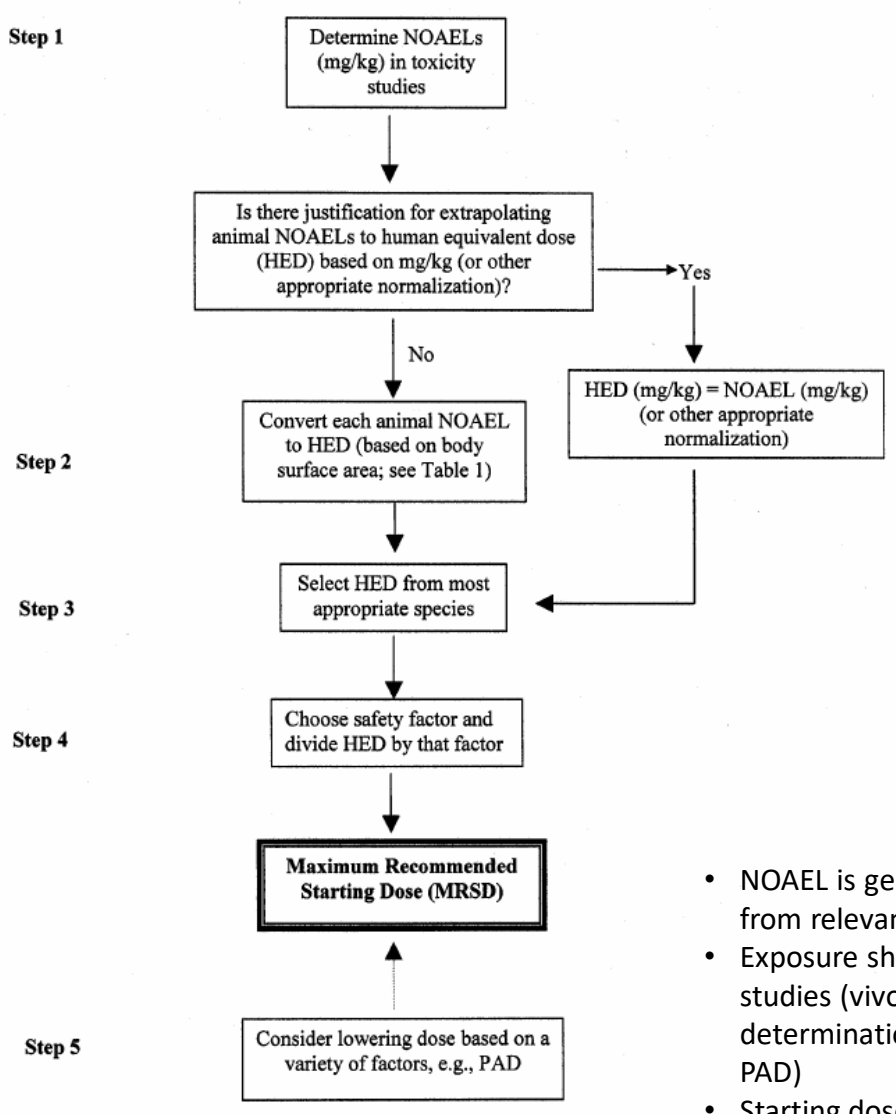
Study design schematics of phase I oncology trials

Thank you –

Any question?

hasnaa.haddouk@sobi.com

FDA Guidance (2005)



EMA Guideline (2017)

Determine NOAEL, MABEL & PAD

↓

Convert to HED

↓

Confirm appropriateness of MRSD

MRSD
HV: < PAD
Patients: ≤ PAD

ICH S9 (2010)
(patients with advanced cancer)

Determine STD10 (Rodents)

Determine HNSTD (Non-Rodents)

↓

Convert to HED

÷ 10 ÷ 6

MRSD

- NOAEL is generally accepted benchmark for safety when derived from relevant animal species
- Exposure showing PD effects in the non-clinical pharmacology studies (vivo, ex-vivo, in vitro) should be determined (to allow for determination of anticipated MABEL in human and estimation of the PAD)
- Starting dose in patients:
  - is expected to have a minimal pharmaological effect
  - Should also take into account the nature of the disease