Grand Challenges
African Drug Discovery Accelerator

Drug Discovery and Development Course

Translation from preclinical to clinical and building an integrated product development plan

Cristina Donini, PharmD, PhD
Medicines for Malaria Venture

Supported by

Gates Foundation LifeArc H3D FOUNDATION

Learning objectives

- Understand what translational science is and its importance in drug development
- Understand the key steps in translating preclinical research to clinical trials
- Understand the challenges
- Gain a broad understanding of what is required for drug development

Start with the end in mind

TPP, Target Product Profile

A strategic document used in drug development to outline the desired attributes of a pharmaceutical product

IPDP, Integrated Product Development Plan

The roadmap that aligns stakeholders, including research, preclinical, clinical development, regulatory, and marketing teams, on the plan to market

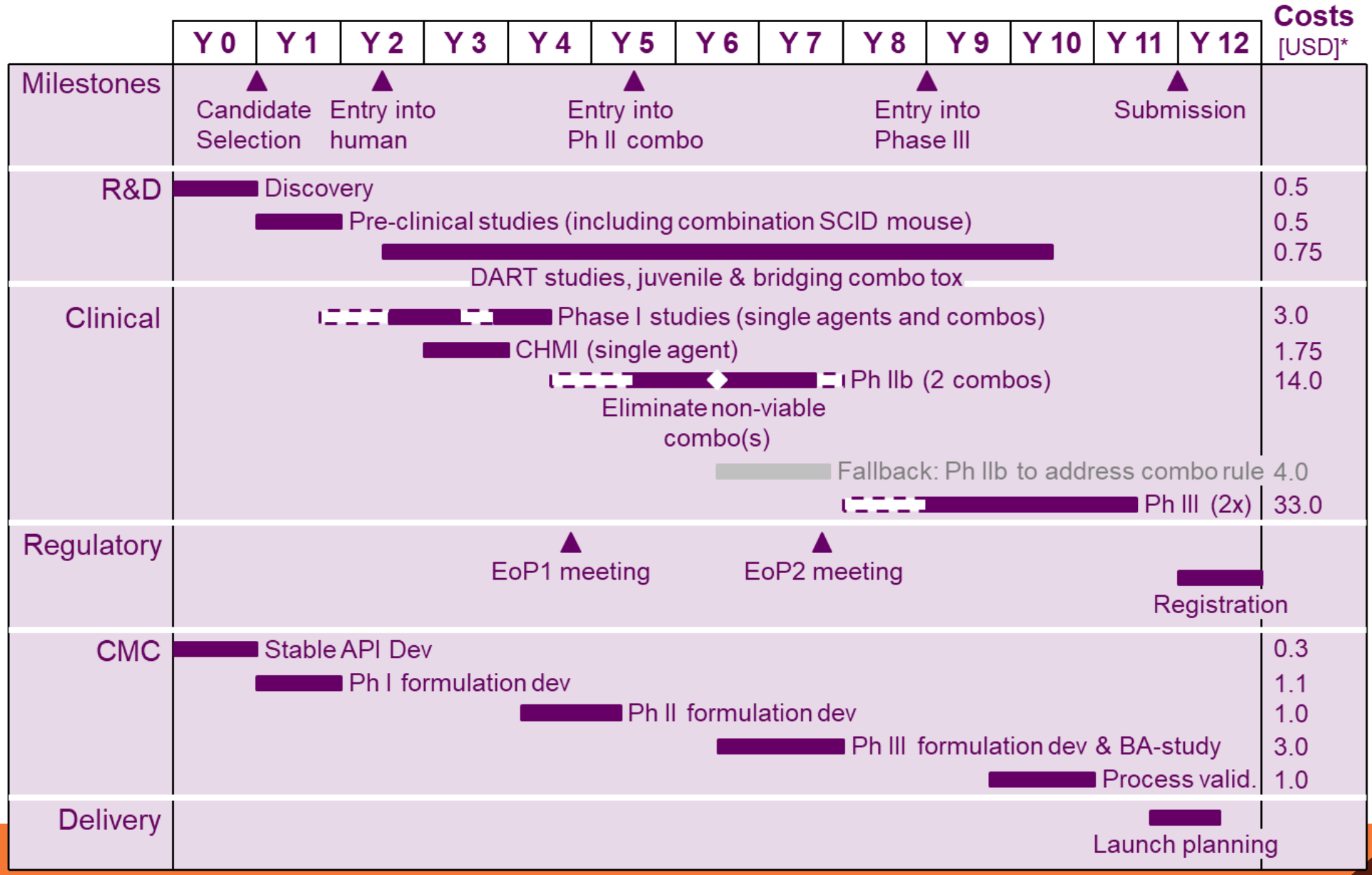
What a TPP can look like

Parameters	Minimum essential (for first registration)	Ideal case (potentially life-cycle management)
Indication for use	Prevention against P. falciparum malaria	Prevention against malaria caused by any Plasmodium species or mixed infection
Target population	**≥5 years**	≥3 months All populations at risk Pregnant women in all trimesters and breastfeeding women Non-immune individuals
Dosing regimen	**Once every 3 months** *(based on preclinical simulations)*	Once every 6 months
Formulation	Intramuscular injection; volume injected and needle size in line with current standard for vaccines; partner drugs can be injected separately	Liquid pre-filled injection device for intramuscular or subcutaneous injection; **fixed dose combination of the drugs** *(based on latest CMC data)*
Antimalarial effects	Two blood schizonticide drugs	**Same as minimum essential + at least one drug with causal prophylactic, gametocytocidal or sporontocidal activities**
Efficacy	**Preventive Efficacy against malaria infections of ≥80% over 3 months** *(based on preclinical PK)* **Clearance of asymptomatic infections** *(based on preclinical)*	Same as minimum essential *Non-immune (and pediatric): preventive efficacy against symptomatic malaria infections ≥80% over 3 months* *Pregnancy: preventive efficacy against malaria infections in the mother of ≥75% over 6 months and ideally, adverse pregnancy outcomes comparable to standard-of-care*
Drug resistance	**Partner drugs with different mechanism of resistance** **Active against known drug-resistant clinical isolates**	Partner drugs with similar pharmacological duration of efficacy
Safety and Tolerability	Favorable risk–benefit profile, with safety and tolerability comparable to WHO recommended preventive treatment or standard-of-care (if any)	Improved safety and tolerability versus WHO recommended preventive treatment or standard-of-care (if any)
Drug–drug Interactions	Minimal interactions manageable with dose adjustments	**No clinically significant interactions (based on SimCyp)**
Cost of treatment course	Equivalent or lower than malaria vaccine	**$1 for infants, $2 for children, $4 for adults**
Stability	**≥2 years at ICH zone IVa/IVb conditions**	≥3 years at ICH zone IVa/IVb conditions

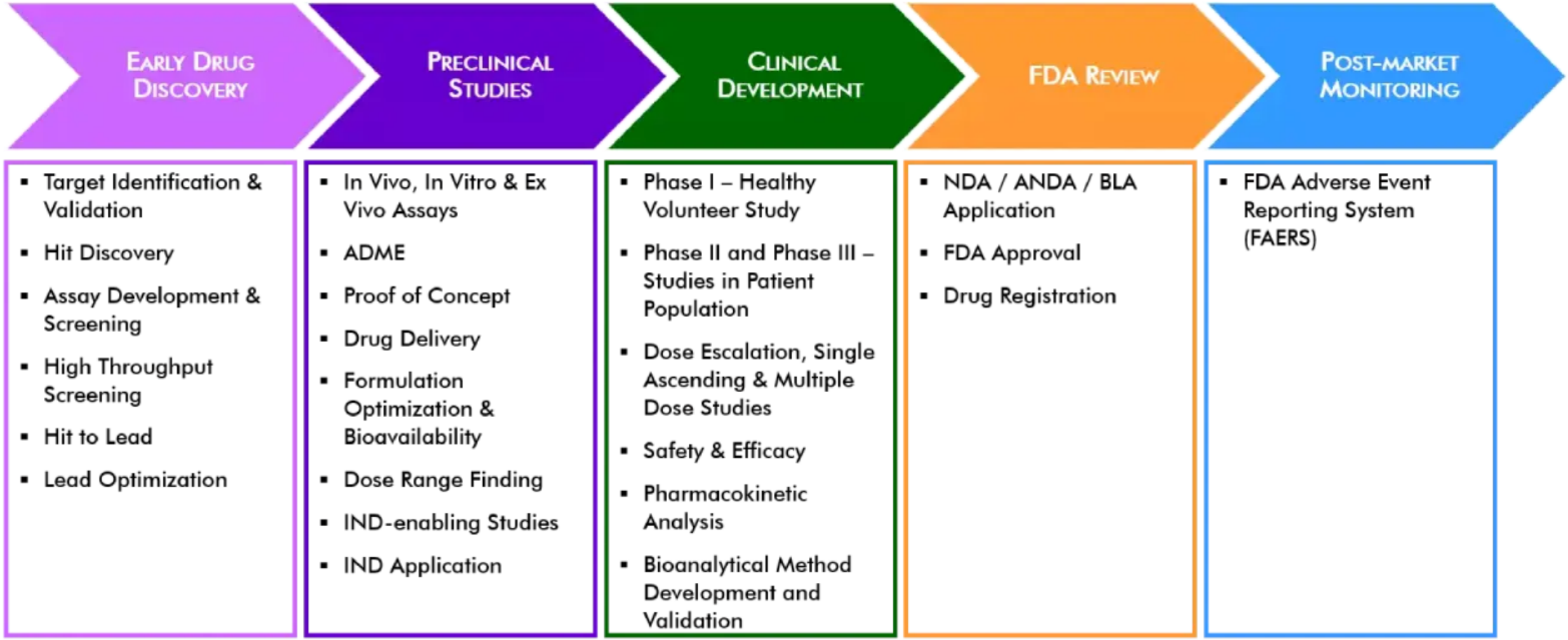
Why is TPP important?

- **Guides Development Decisions**: Helps teams prioritize research activities based on the product's ultimate goals.
- **Risk Mitigation**: Helps identify potential gaps or challenges early in the development process.
- **Cross-Functional Alignment**: Ensures consistency across research, development, and marketing strategies.
- **Regulatory Alignment**: Provides a structured framework for discussions with regulatory agencies, such as the FDA or EMA.

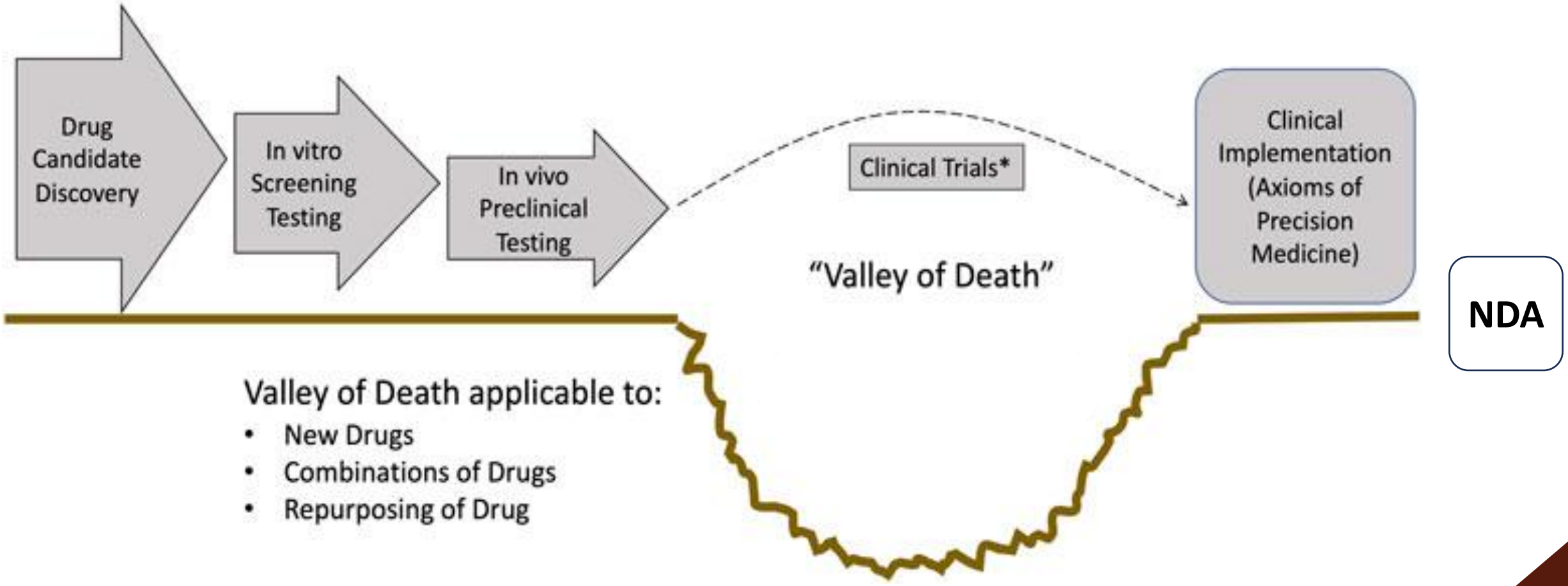
What an IPDP can look like



What does it take to get to a product?

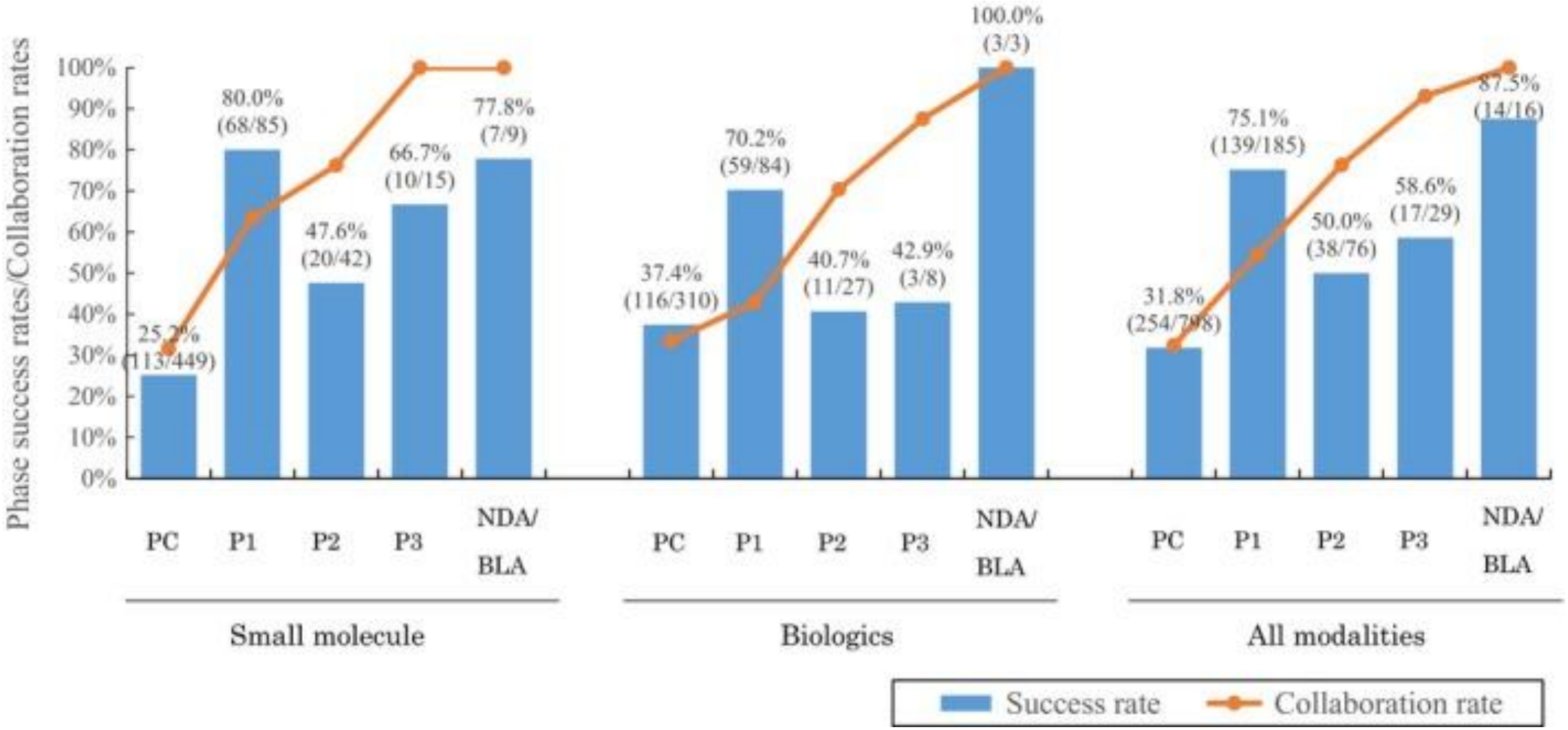


Translational gap: the “valley of death”

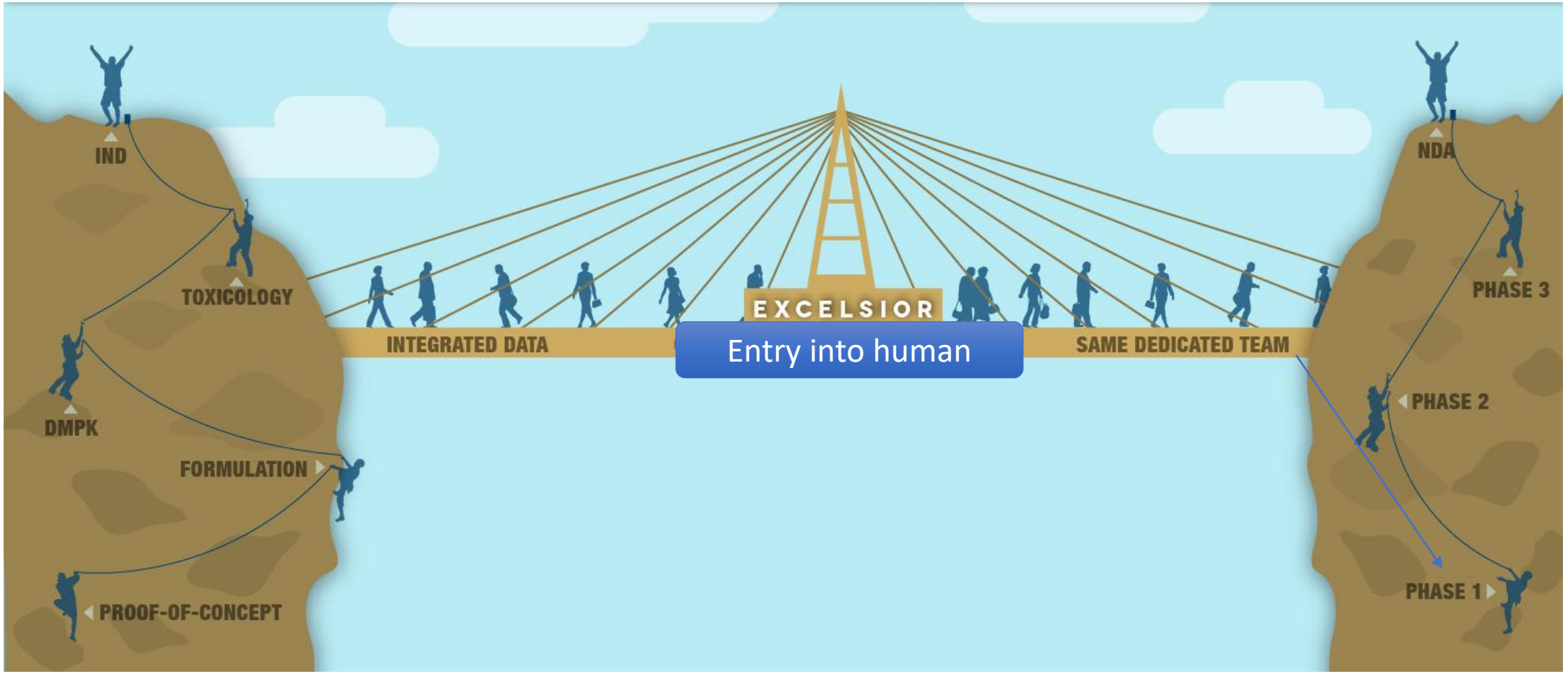


Front. Syst. Biol., 28 April 2022
Sec. Translational Systems Biology and In Silico Trials
Volume 2 - 2022 | https://doi.org/10.3389/fsysb.2022.901159

Translational gap: the “valley of death”



Bridging the gap between preclinical and clinical



Preclinical development:
Demonstrate proof of concept and ensure safety before human trials.

Clinical development:
Assess safety, tolerability, PK, and later efficacy in Ph2 and Ph3

Preclinical development

Goal: gather data that supports the **safety and potential effectiveness** of the drug before testing it in humans.

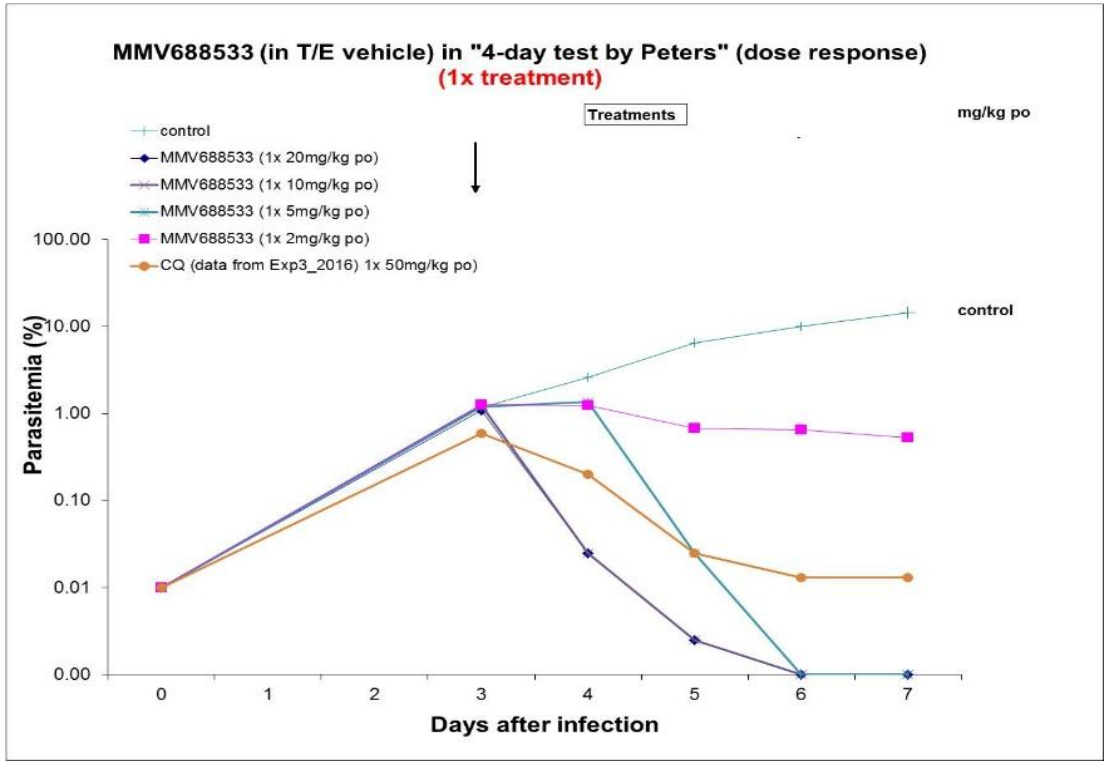
Key Studies:

- Pharmacokinetics (PK) and pharmacodynamics (PD)
- Toxicology studies (acute, sub-chronic, chronic)
- *In vitro* and *in vivo* models

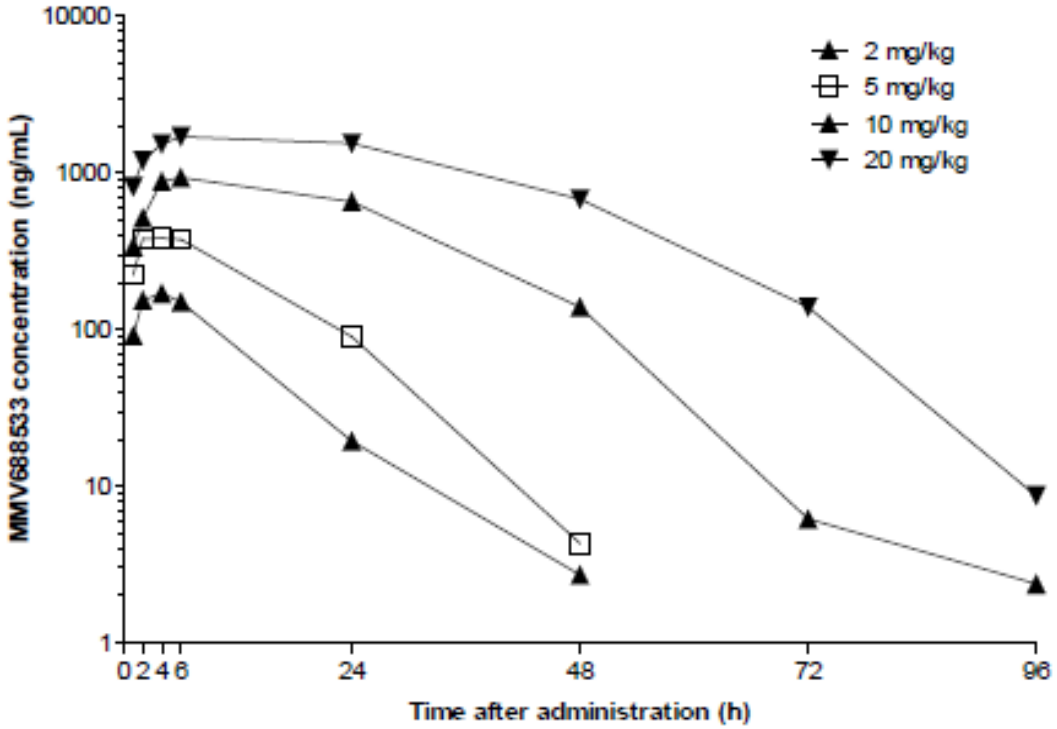
Go/No-Go Decision Criteria: therapeutic window, toxicity thresholds, meet TPP

Building the bridge

- Animal model to assess the pharmacodynamics (PD)



- Dose response in animal to assess pharmacokinetics (PK)



Building the bridge

- GLP toxicity studies to **assess the safety profile of the molecule**
- Studies in rodents and non rodents
- **Regulatory guidelines** to be followed (ICH M3 (R2), FDA/EMA)
- **Important considerations when designing a GLP tox package before FIH:**
  - What is your intended indication? Disease? Treatment? Prevention?
  - What is the intended clinical duration? Acute (single dose), sub.chronic, chronic
  - What is the route of Administration(Match the intended clinical administration route oral, IV, im, sc, etc.)

- **Safety Endpoints**
- Toxicokinetics: Assess systemic exposure and bioavailability.
- Clinical Observations: Behavioral changes (CNS), body weight, and clinical signs.
- Hematology and Clinical Chemistry: Assess organ functions.
- Histopathology: Evaluate tissue changes post-mortem.
- Safety Pharmacology: Address cardiovascular, respiratory, and CNS risks if not covered in tox studies.
- Developmental toxicity: assess potential use in pregnancy
- Carcinogenicity studies for chronic indications

Translation: predicting the human

Modelling & simulation

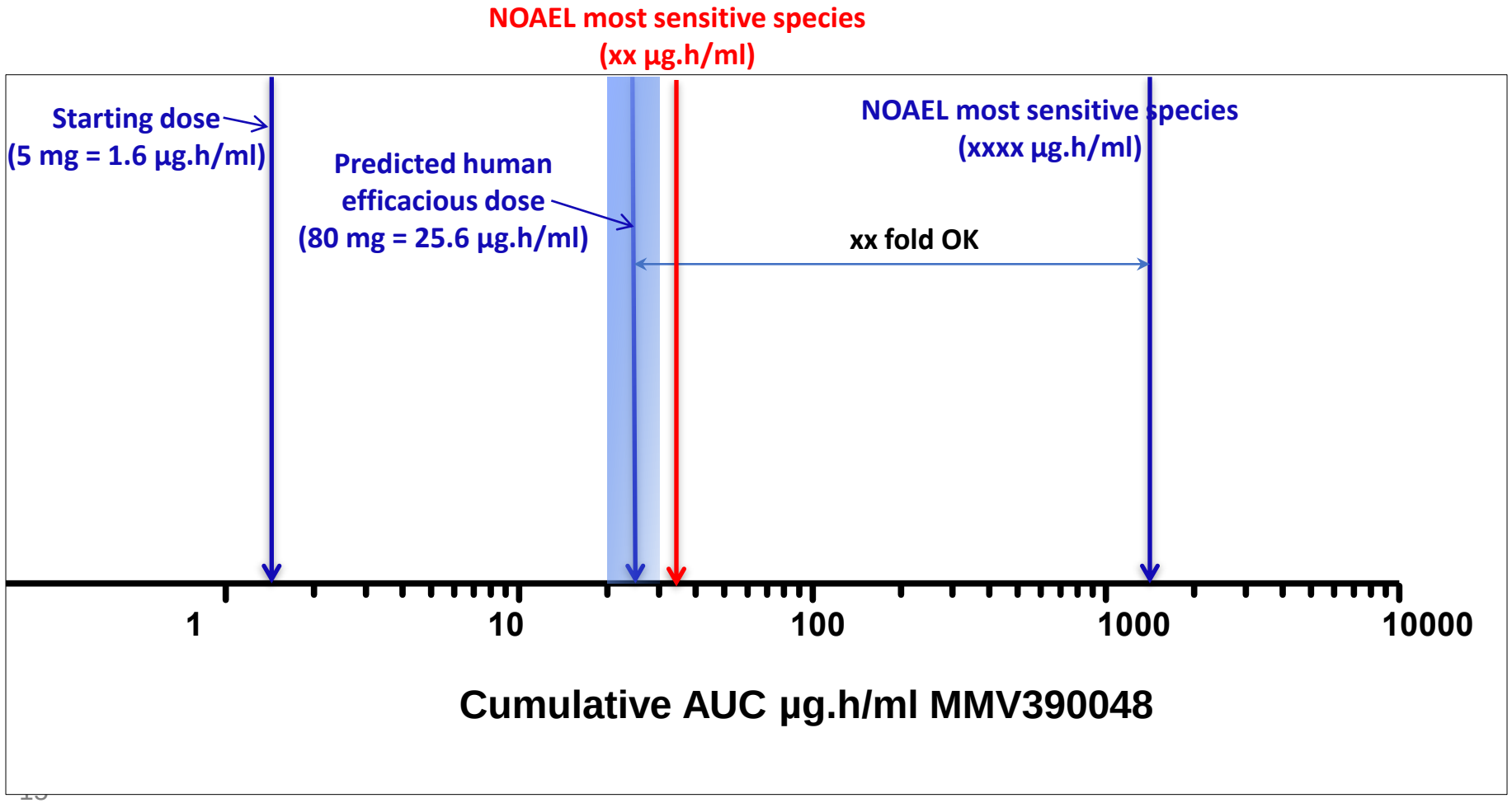
Innovative quantitative tools and modelling methods to inform dosing, combo choice, etc. (e.g., advanced PK/PD models)

Predicted Human efficacious dose

Human PK parameters

Human safety margins

Safety margins calculation



Go/No go criteria to entry into humans

THINK ABOUT YOUR TPP

Go/No go criteria to entry into humans

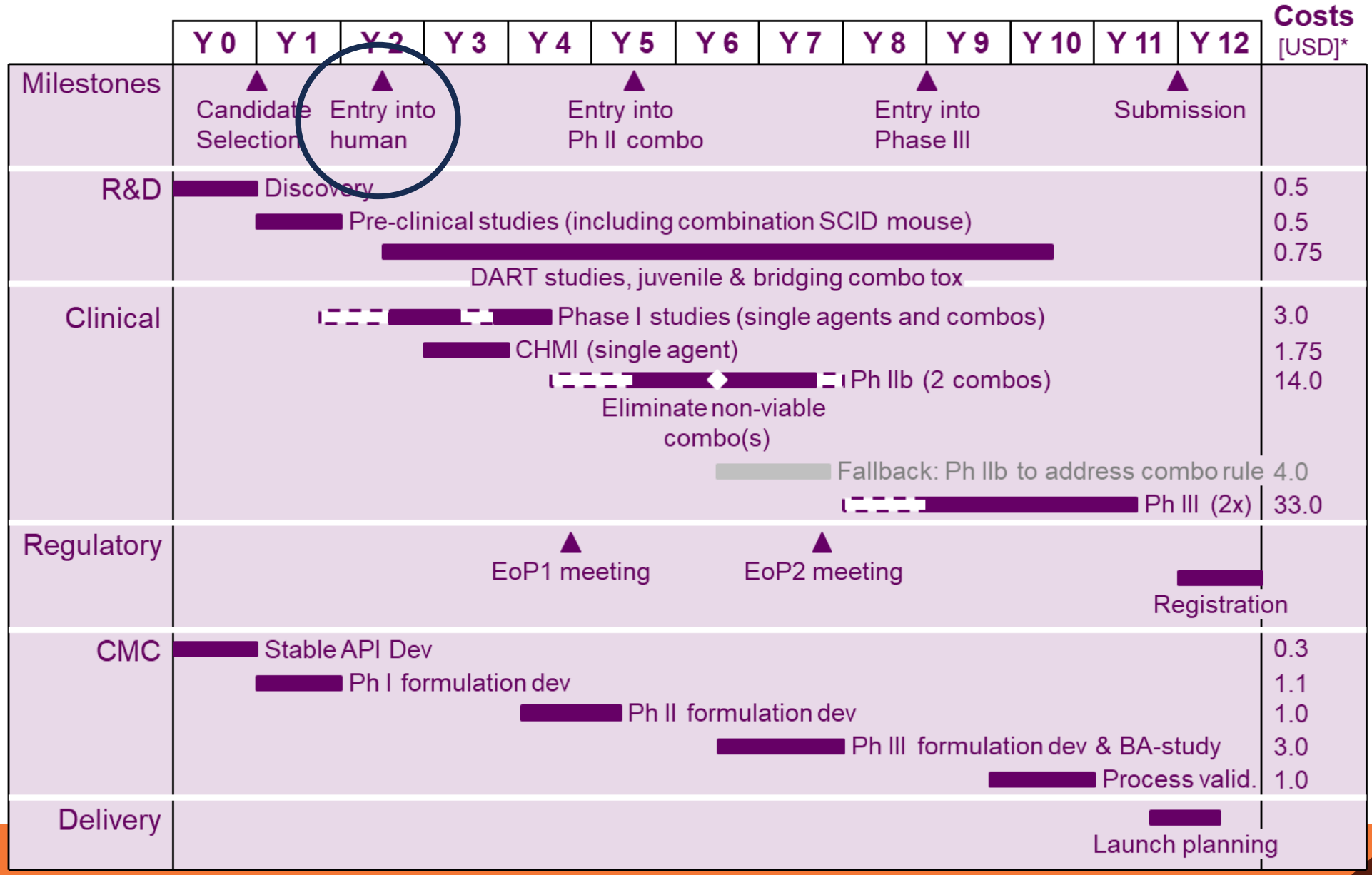
- **Is the predicted human efficacious dose in line with TPP?**
- **Are the safety margins acceptable?**
- **What is the tox profile? Target organs, monitorable, reversible**

Other considerations which won't affect entry into human but should be assess :

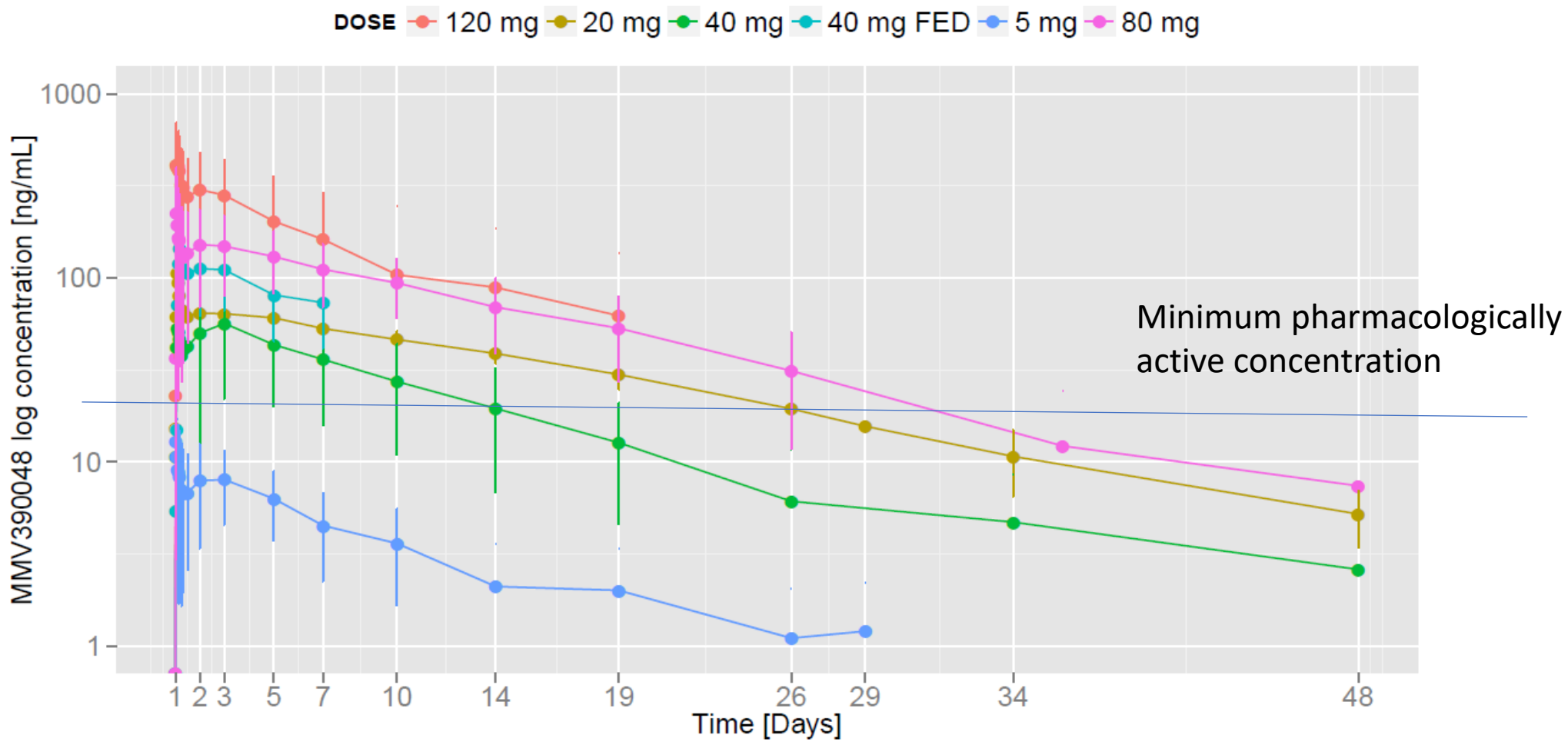
- Drug sustance (ease of production, cost of goods, stability, etc..)
- Drug product (powder in bottle, tablet, child friendly formulation, stability, cost of goods, etc…)

FiH: First in Human

IPDP update


Y 0
Y 1
Y 2
Y 3
Y 4
Y 5
Y 6
Y 7
Y 8
Y 9
Y 10
Y 11
Y 12
Costs [USD]*
Milestones
Candidate Selection
Entry into human
Entry into Ph II combo
Entry into Phase III
Submission
R&D
Discovery
0.5
Pre-clinical studies (including combination SCID mouse)
0.5
0.75
DART studies, juvenile & bridging combo tox
Clinical
Phase I studies (single agents and combos)
3.0
CHMI (single agent)
1.75
Ph IIb (2 combos)
14.0
Eliminate non-viable combo(s)
Fallback: Ph IIb to address combo rule
4.0
Ph III (2x)
33.0
Regulatory
EoP1 meeting
EoP2 meeting
Registration
CMC
Stable API Dev
0.3
Ph I formulation dev
1.1
Ph II formulation dev
1.0
Ph III formulation dev & BA-study
3.0
Process valid.
1.0
Delivery
Launch planning

What does a PK curve in human look like?



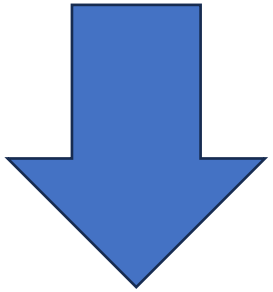
First stress test on translation is First in HumanTrial (FiH)

- **Safety** in human is the primary objective (was preclinical toxicity predictive of human safety?
- Pharmacokinetic needs to be confirmed

Cohort	Dose (mg)	Predicted Cmax	C_{max} (µg/ml)	Predicted AUC	$AUC_{0\text{-}inf}$ (µg.h/ml)	C_{max} Margin	$AUC_{0\text{-}inf}$ Margin
A1 (fasted)	5		0.021		1.60	345	94.9
A2 (fasted)	20		0.085		6.41	86.2	23.7
A3 (fasted)	60		0.254		19.22	28.7	7.91
A4 (fasted)	120		0.508		38.44	14.4	3.95
A5 (fasted)	220		0.932		70.46	7.83	2.16
A6 (fasted)	340		1.440		108.9	5.07	1.40
A7 (fasted)	500		2.118		159.8	3.45	0.95
A8 (fed)	TBD		-		-	-	-

Go/No go criteria to next clinical phase

- **Is the PK in line with predicted PK? Think if you need to change formulation, and go back to your TPP?**
- **Is safety and tolerability acceptable? Think about your indication, go back to your TPP**



POC: Proof of Concept (either challenge model or patient exploratory)

Human Proof of Concept (PoC)

Refers to an early-stage clinical study designed to **determine** whether a drug or therapeutic intervention demonstrates **initial evidence** of biological activity and **clinical efficacy** in humans. The goal is to confirm that the drug has the potential to achieve its intended effect in the target patient population or healthy volunteers.

Key Objectives:

- **Efficacy**: Evaluate whether the drug shows meaningful biological or therapeutic activity.
- **Safety**: Assess the drug's safety and tolerability in a limited population.
- Pharmacokinetics (PK) and Pharmacodynamics (PD): Understand how the drug behaves in the body and its mechanism of action.
- **Dose Optimization**: Identify dose ranges for further clinical development.

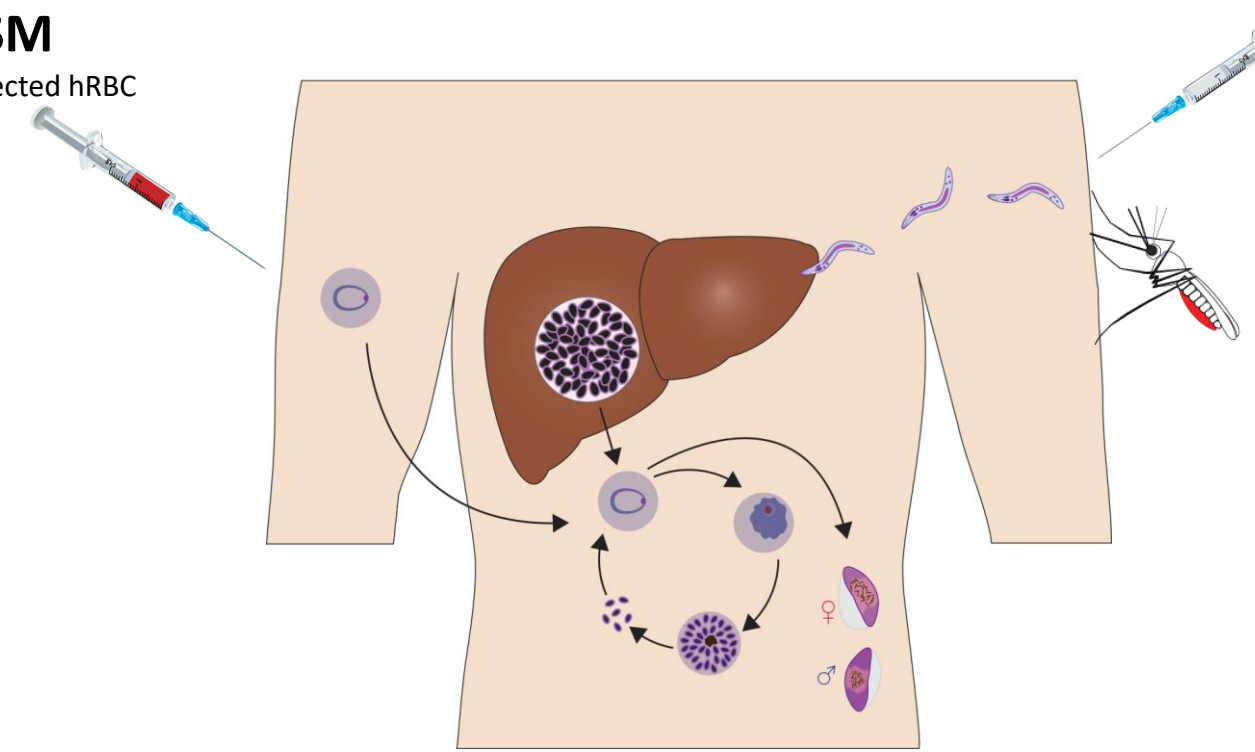
Volunteer Infection Studies (VIS)

Efficacy is the primary objective

And safety

IBSM

2800 *Pf* infected hRBC



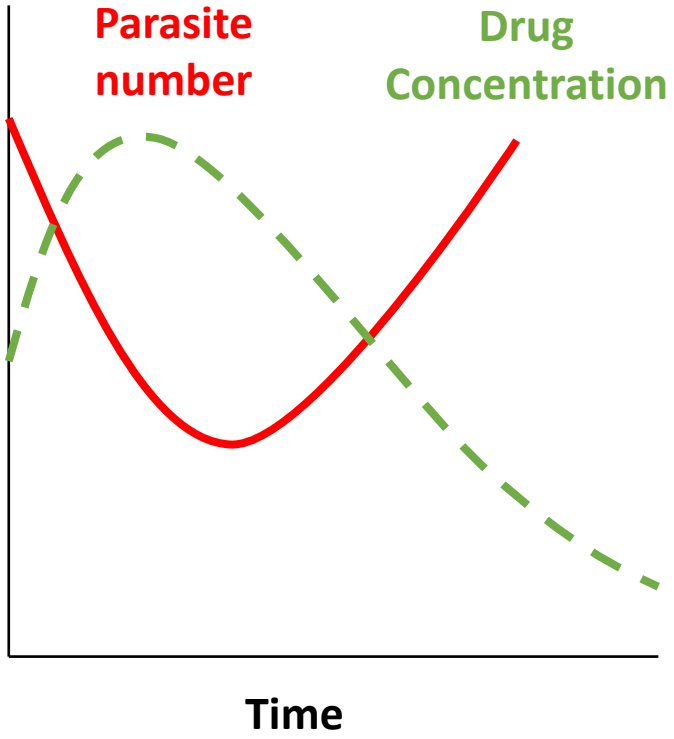
SPZ-VIS

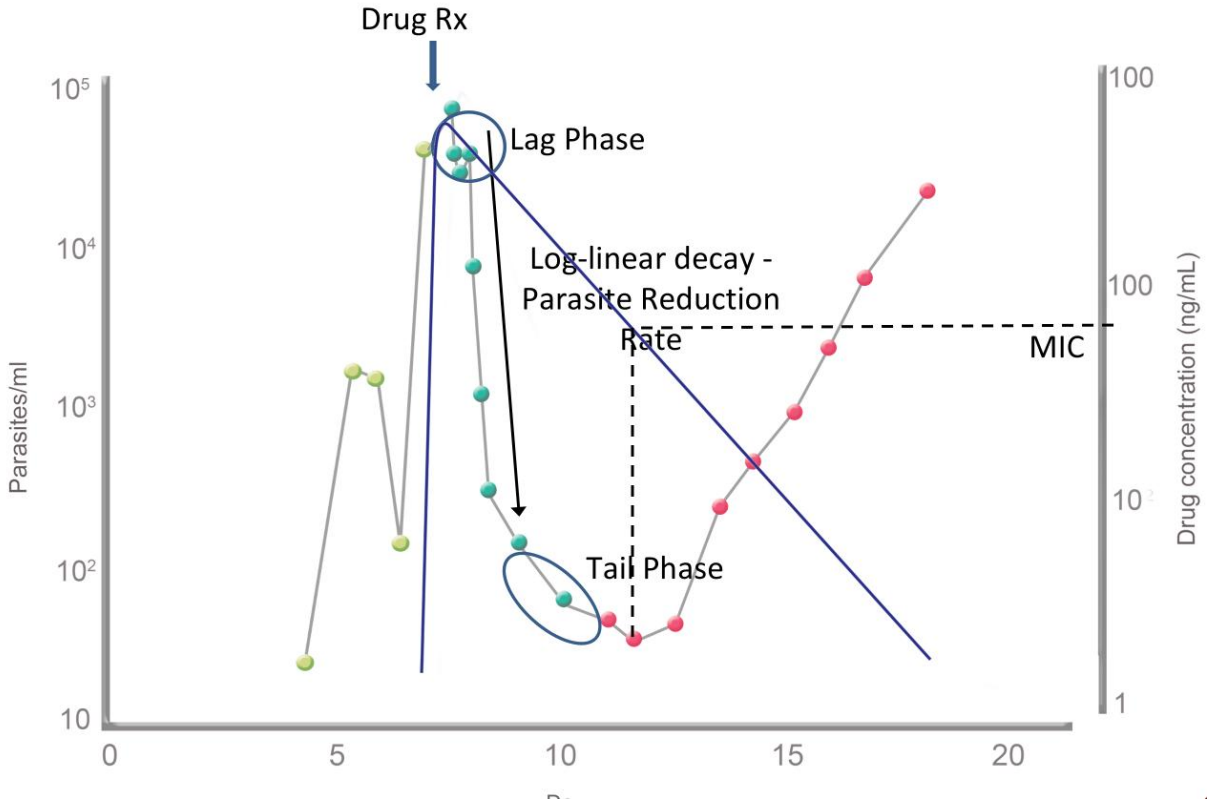
Cryopreserved
SPZ (3200) from Sanaria

SPZ-VIS

Mosquito-bite
(~100 SPZ)

Using pharmacometric modelling: Combining PK and PD

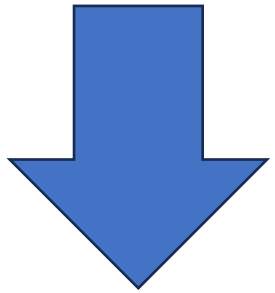




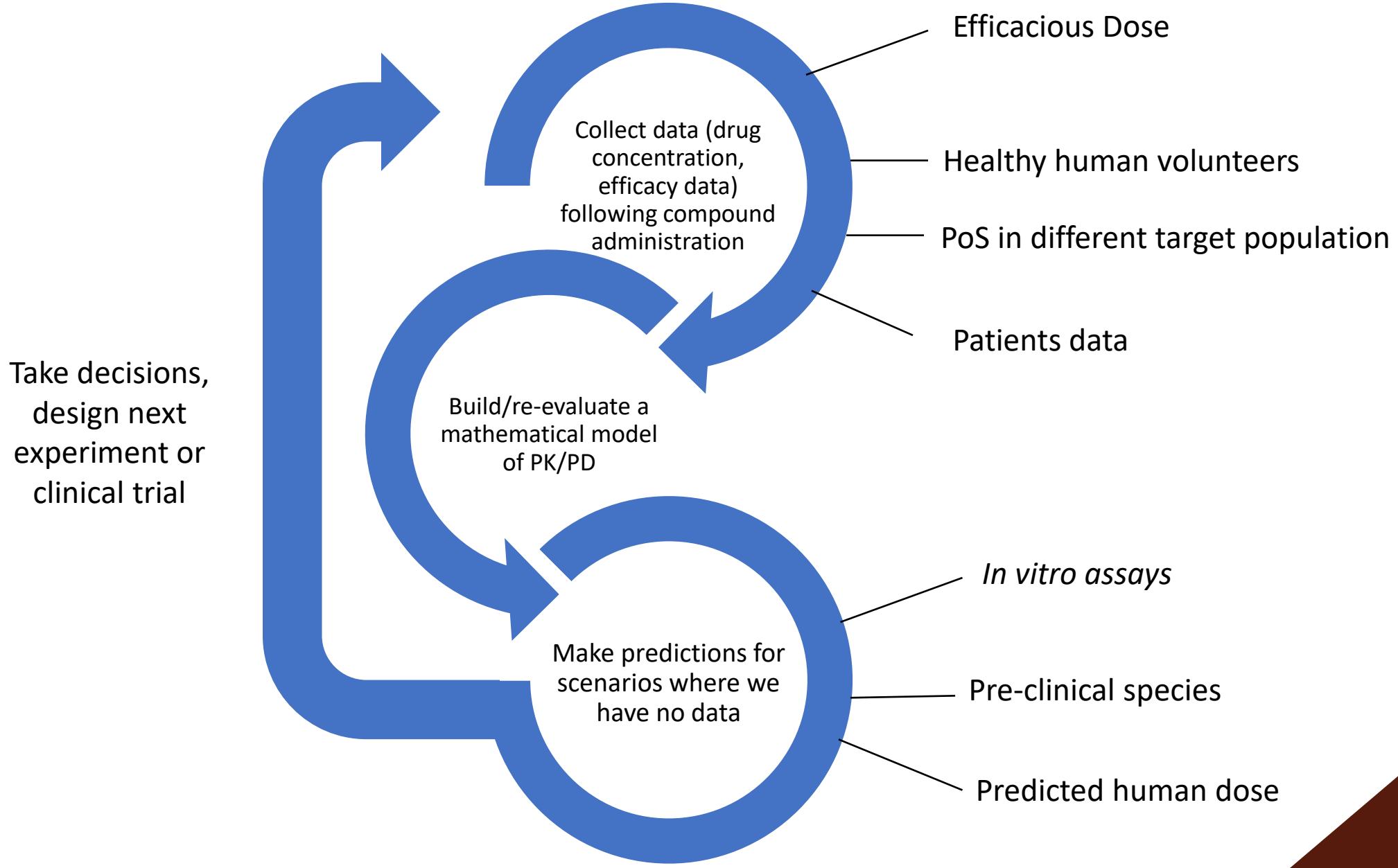
Combining PK and PD from human studies
recalculate human efficacious dose to meet TPP

Go/No go criteria to next clinical phase

- **Is the efficacy in line with the one expected from preclinical data? Do you meet the TPP criteria?**
- **What is the Probability of Success (PoS) of reach your efficacy goal in the next clinical phase? (PKPD modeling)**
- **Is safety and tolerability acceptable in your patient population? Think about your indication, go back to your TPP**



Patient confirmatory study (Ph2b/Ph3 – bigger sample size)


Efficacious Dose
Collect data (drug concentration, efficacy data) following compound administration
Healthy human volunteers
PoS in different target population
Patients data
Take decisions, design next experiment or clinical trial
Build/re-evaluate a mathematical model of PK/PD
In vitro assays
Make predictions for scenarios where we have no data
Pre-clinical species
Predicted human dose

Early Development

Preclinical

Human volunteers

Development of combinations

Product development

Patient exploratory

Patient confirmatory

Data

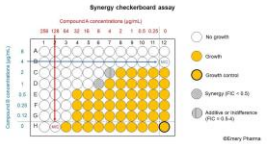
In vitro assays

Animal experiments

First in Human (PK)

Volunteer infection (PK + PD)

In vitro combination checkerboard



Phase 2 trials + Interaction studies

Phase 3 non-inferiority trial against standard of care

Model

Many assumptions

Fewer assumptions

First parameterization of combination

Some IIV explained by covariates

Monotherapy PK+PD

In silico combination

In vivo combination PK+PD

Parameters better defined. Initial estimate of IIV.

Sensitivity analysis of drug-drug interaction

IIV and RSE reduce

Better estimation of drug-drug interactions

Decision

E.g. Uncomplicated Malaria Treatment:

predict the probability of success once on the market

(probability to reach the WHO target of 95% ACPR28* in African children)

* Adequate Clinical and Parasitological Response on Day 28

Next step

Decide doses to be tested in First in Human and Volunteer Infection Studies

Decide dose ratio and doses to be tested in patients

- Adjust doses in special population if needed (eg children)
- Probability of success in phase 3 trial

Key take-aways

Translational science is key in drug development

- Guides the selection of drug candidates with a higher probability of clinical success.
- Uses predictive models to screen compounds for safety, efficacy, and pharmacokinetics.
- Enables early decision-making on dose selection and trial design.
- Helps in identifying early signals of efficacy or toxicity to guide adaptive clinical trials.
- Reduces late-stage attrition by identifying potential safety or efficacy concerns before Phase 3 trials.
- Informs go/no-go decisions early in the development process.

Grand Challenges
African Drug Discovery Accelerator

THANK YOU

Supported by

Gates Foundation

LifeArc

H3D FOUNDATION