# From animal to *in silico* to humans: clinical trial simulations as a tool for optimisation of Phase I studies with antitubercular drugs.

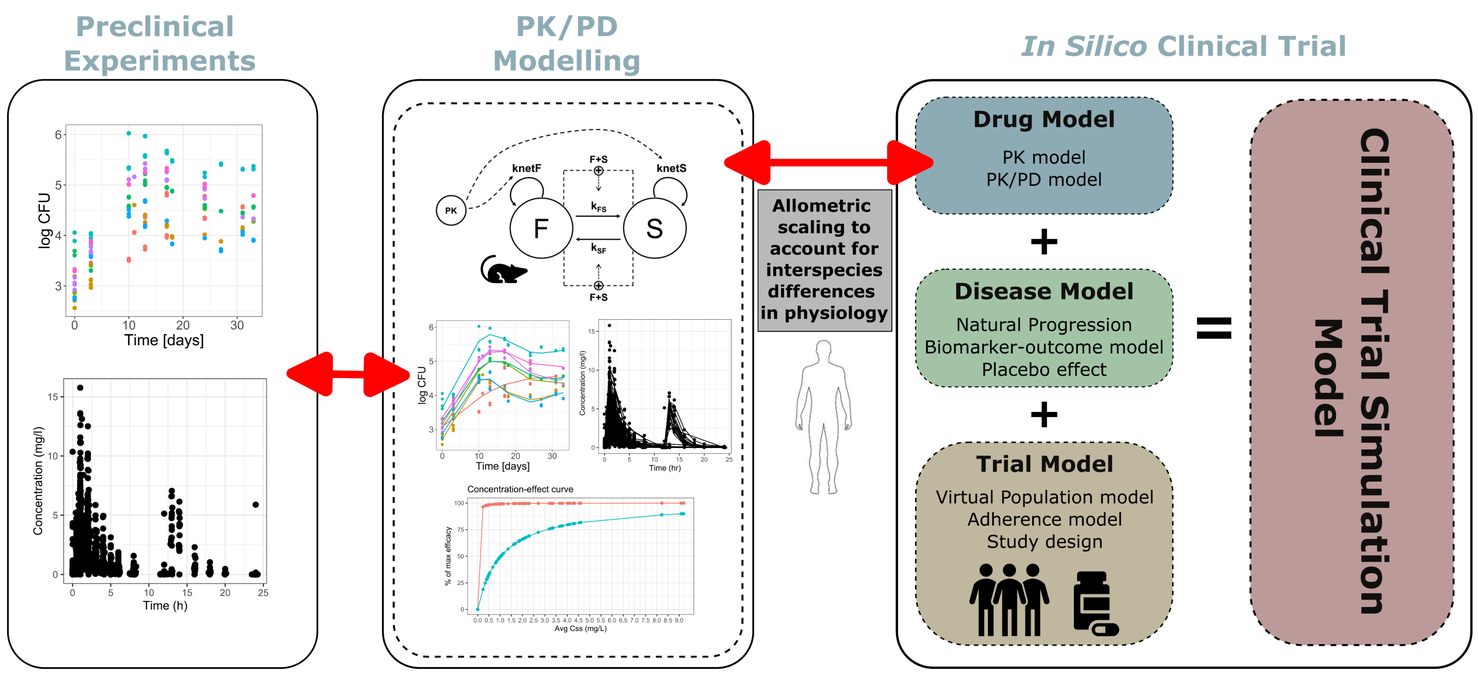
**Umberto Villani[1,2], Silvia Grandoni[1,2], Oscar Della Pasqua[1,2]**

[1] Clinical Pharmacology & Therapeutics Group, University College London, London, United Kingdom, [2] Istituto per le Applicazioni del Calcolo, National Research Council, Rome, Italy

## BACKGROUND & AIM

- The evaluation of a novel medicinal product in humans is a major milestone in drug development. In fact, guidelines have been developed on strategies to mitigate risks for first-in-human (FIH) and early clinical trials with investigational compounds {1}. Defining the dose rationale, including a pharmacologically relevant range in a FIH study is as critical as the concerns about the tolerability and overall safety profile of the candidate compound in humans.
- Clinical trial simulations (CTS) can be used to reproduce *in silico* an unlimited number of experimental scenarios. These scenarios can be then systematically investigated to identify the appropriate dose range as well as the most suitable design, integrating pharmacokinetic (PK), pharmacodynamic (PD) and safety data.
- The use of CTS as an optimization tool has been recognized across many therapeutic areas {2}. However, its potential has yet to be harnessed in the development of antitubercular drugs, where the human dose selection has mostly remained empirical {3}.
- **Here we illustrate how CTS can be use as a tool for the optimisation of Phase I single/multiple ascending dose studies with antitubercular drugs.**

## METHODS

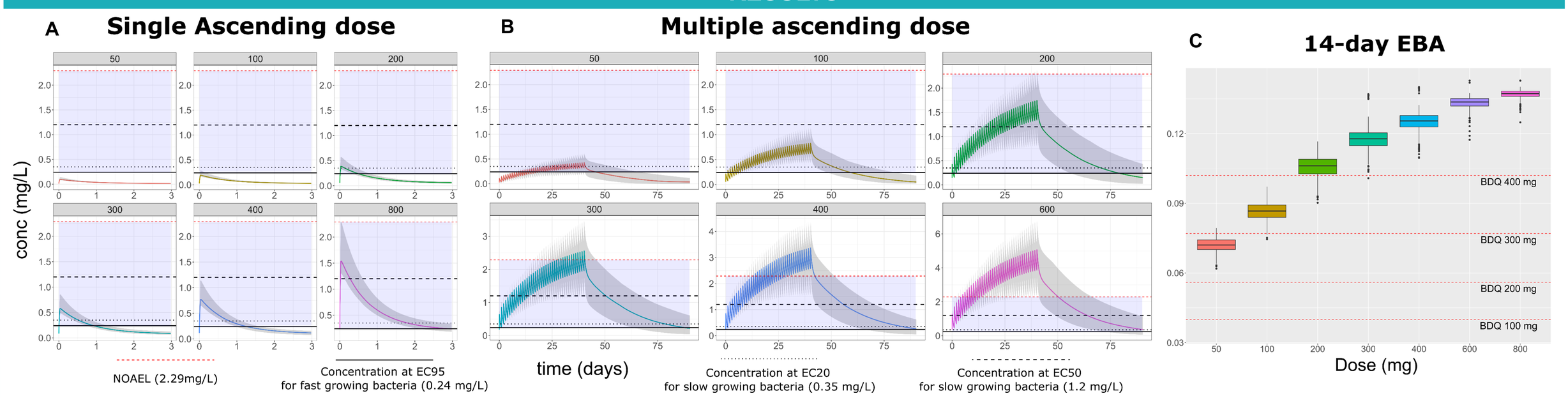



CTS is a comprehensive framework featuring three distinct modules: a drug model, a disease model, and a trial model.

The **drug model** describes the drug's pharmacokinetics and its pharmacodynamic properties. This information is identified throughout extensive preclinical testing. Modelling of these data enables subsequent scaling and prediction of drug disposition and pharmacodynamics in humans. Allometric scaling is often used with maturation principles for this purpose {4}. The **disease model** primarily describes the time course of the underlying pathology, and the relationship between PD (i.e., biomarker) and clinical outcomes. When appropriate, a placebo effect model can also be incorporated into this module. Finally, the **trial model** dictates the features of every simulation scenario, including details on treatment, statistical design and study population, i.e., virtual subjects whose demographic and clinical characteristics reflect actual human subjects.

To illustrate the potential of CTS for the design of Phase 1 FIH studies for antitubercular drugs, a novel diarylquinoline derivative (TBAJ-587) currently in development by TBAlliance is used as paradigm compound {5}. TBAJ-587 shows greater *in vitro* potency and reduced cardiovascular liability than Bedaquiline (BDQ) {6}. These properties make TBAJ-587 a promising candidate for inclusion in modern multidrug regimens for MDR-TB. The challenge is the anticipated long half-life and potential contribution of active metabolites to the overall antitubercular activity.

## RESULTS




CTS provides insight into the exposure (concentration vs. time) profiles for TBAJ587 at different dose levels based on in vitro and in vivo estimates of the antitubercular activity against *M. tuberculosis*. Here simulation scenarios are used to select the dose levels to be tested in SAD (panel A) and MAD (panel B) regimens in a Phase I study. Additionally, a drug-disease model was used to predict the 14-days antibacterial activity (EBA) in patients, taking into account different sources of variability in a clinical setting (Panel C). Each dosing scenario was obtained from a trial model, in which patient-specific characteristics and covariates are included.

In the SAD study, peak concentrations (Cmax) were lower than safety threshold (e.g. NOAEL), suggesting that doses higher than 800 mg may not be tolerated or safe. On the other hand, a meaningful starting dose seemed to be 200mg, which corresponds to peak concentrations associated with efficacious levels for eradication of the fast-growing subpopulation of bacteria. In this regard, the use of CTS also reveals that at 800mg dose one may not achieve full eradication of less susceptible subpopulation (i.e., slow-growing *M. tuberculosis*).

Moreover, these scenarios provided evidence of the potential implications of daily dosing with TBAJ-587, as it has a very long terminal half-life (range: 338-407 hours). Such a half-life imposes a parallel design for a MAD study. It also raises the question about the need and relevance of a loading dose, given the time required to reach steady state (SS). Another aspect of a drug with long half-life is the accumulation when doses are to given over a period of up to 6 months in subsequent clinical studies. In this exercise, the starting dose at 50mg reaches therapeutic concentration at SS, while doses above 200 mg could be associated with potential tolerability issues.

## CONCLUSIONS

- CTS enables integration of pharmacokinetic, pharmacodynamic, safety and toxicology data in a systematic manner. Through simulation scenarios it is possible to optimise clinical trial design, including sample size, treatment duration, companion drug selection and dose rationale.
- While model-informed drug development has gained acceptability within regulatory bodies and has become standard practice in industry, its application for the evaluation of novel antitubercular compounds remains limited.
- We advocate the use of CTS as a tool for a more efficient evaluation of antitubercular compounds in clinical development. A critical feature of simulations is the possibility of predicting not only drug exposure but also the overall antibacterial activity of compounds following administration as monotherapy or combination therapy.

## REFERENCES

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**Contact: u.villani@iac.cnr.it**