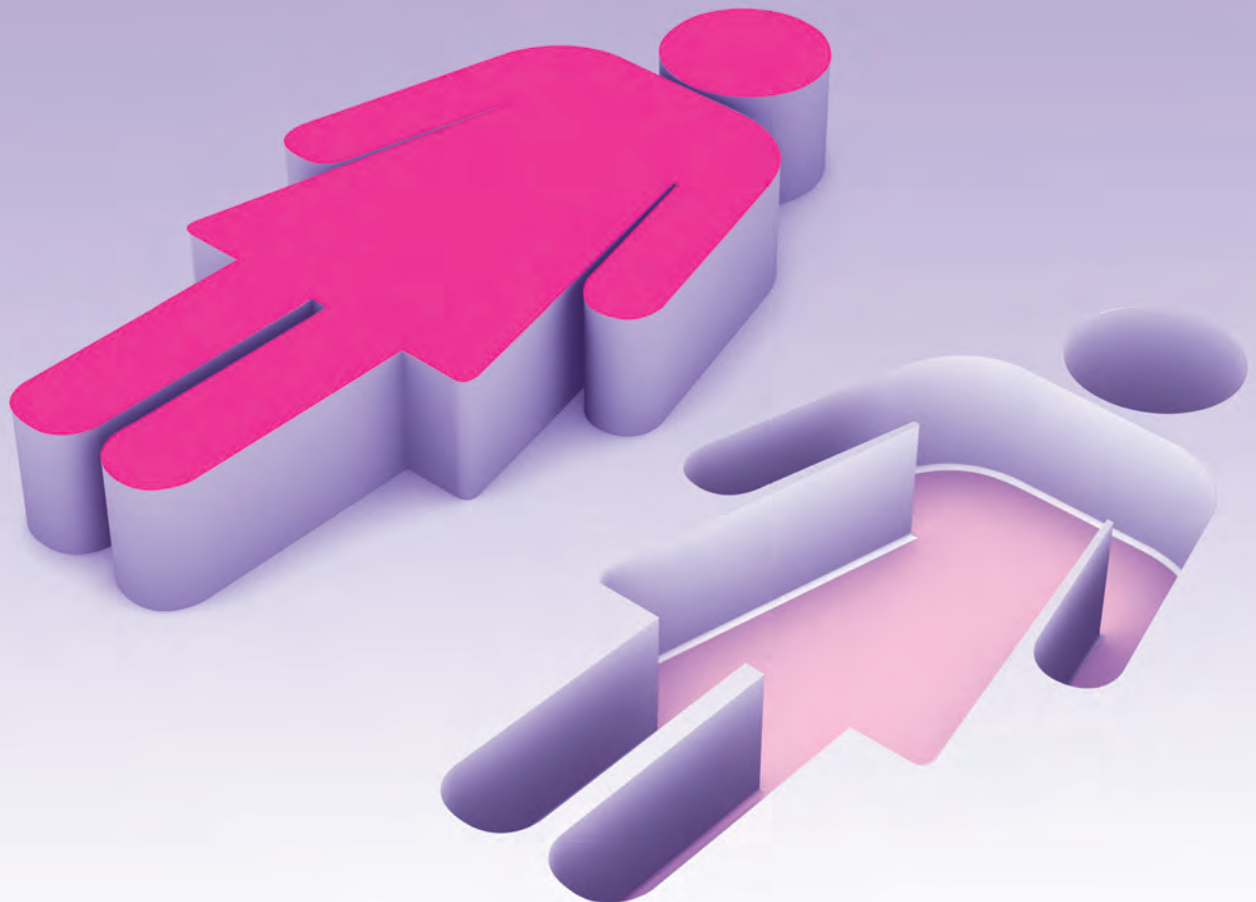abpi

Bringing medicines to *life*

Clinical trial simulations – an essential tool in drug development

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Preface

The clinical development of investigational drugs is a complex and expensive process. The costs can be affected by decisions that are taken as clinical trials progress from one stage to the next (eg. dose selection studies and transitions from Phase 2 to Phase 3 clinical trials). Clinical trial simulations are being increasingly viewed as an integral part of clinical development programmes and can be used to improve the understanding and decision making at every stage of drug development. In this article we provide an example led overview illustrating the impact that simulations can have along the drug development timeline.

Introduction

Pharmaceutical companies invest huge amounts of money and time into the clinical development of medicines, yet only 10% of candidate drugs that enter clinical studies are ultimately approved.[1] For those that do reach the market, the clinical development process can take around a decade. Therefore, improving the success rate and accelerating clinical development are top priorities for both pharmaceutical companies and regulatory authorities. This ideal is being compromised by the current "compartmentalised phases" approach used to assess the safety and efficacy of candidate drugs which have not kept up with the pace of scientific change. One technology that has been identified by many regulatory agencies as being underutilised by medicine developers is the use of clinical trial simulation. Regulatory agencies see this tool as an essential part of drug development, as evidenced by the increase in the number of guidelines and initiatives released over recent years.[2-7]

What is a clinical trial simulation?

In its simplest form, a clinical trial simulation is the study of the effects of a drug in virtual patient populations using mathematical models that incorporate information on physiological systems. The virtual patient population is selected to fit certain characteristics (eg. age, disease status, ethnicity) that are relevant for the study of a particular drug–patient combination that is under investigation. The purpose of a clinical trial simulation is to help understand the likely impact of some of the unknown factors (eg. endpoint variability, recruitment and drop out, treatment effects) that might occur in the actual clinical trial. Simulations can also be performed with differing scenarios (eg. different sized efficacy outcomes) to define the optimal study design of the clinical trial and the target patient population. This can help to give an idea of whether that design is sufficiently powered to determine a clinical benefit. Simulations are particularly useful in areas where clinical testing raises special concerns, such as in children or in pregnant women.

As we shall discuss, clinical trial simulations can be used to quantify uncertainty about dose selection and other key issues related to drug safety and efficacy. Consequently, it should be possible to predict the results in actual clinical trials with greater certainty, perhaps reducing the number of patients studied and the number of endpoints assessed in clinical studies. This will improve the efficiency of clinical development. Importantly, sponsors are also more able to make informed decisions on when to remove a product from development, so reducing patient exposure to an effective study drug as well as lowering overall development costs.

The purpose of this paper, a collaboration between members of the Association of the British Pharmaceutical Industry (ABPI) and Statisticians in the Pharmaceutical Industry (PSI), is to provide examples of clinical trial simulations across all phases of drug development, with the specific aim of raising awareness and encouraging its wider use, which will ultimately increase the efficiency of the drug development process.

Clinical pharmacology

Clinical pharmacology studies range from early first-in-human studies to studies that are ultimately expressed on the drug label to describe how the drug is to be used with respect to intrinsic factors such as age, gender, renal function and race, and extrinsic factors such as administration with food and other drugs.

First-in-human studies

In preparation for a first-in-human study, simulations may be based on allometry (the relationship between body size and drug disposition) and are of value in setting a safe starting dose, especially for small molecular mass chemical entities. Such simulations are usually based on pharmacokinetic parameters from at least three different species.[8] The allometric relationship between actual pharmacokinetic parameters and body mass in the pre clinical species enables the extrapolation to species that have a larger body mass (ie. humans), aiding the selection of a safe starting dose with acceptable pharmacological activity.

Physiologically based pharmacokinetic models (PBPK) can be used to simulate human pharmacokinetic parameters such as clearance of the drug from the body as well as pharmacokinetic profiles. Commercially available software is widely used in industry and its use is based on knowledge of biology and population as well as specific information on the drug.[9-11] Such simulations require data on the physico chemistry of the drug, in vitro metabolic stability (eg. in human hepatocytes), and information related to drug absorption and active transport. The software systems contain databases of virtual patient populations and include information such as body weight, race, genetic polymorphisms and age. An example of the outcome of a PBPK model is shown in Figure 1a, which shows that the profile of simulated and actual plasma concentrations of a drug that is cleared principally by cytochrome P450 3A-catalysed metabolism.

During the course of a dose escalation study, simulation can be used to help decide the most appropriate next dose or dose regimen. Methods used in this type of simulation may involve use of dose versus clearance regression models, simple superposition models and compartmental models. An example simulation is presented in Figure 2,[12] which simulates the pharmacokinetic profile of a drug that would be seen after

multiple daily administration. Such simulations help determine the optimal dose and dose regimen to achieve a target plasma exposure and time concentration-time profile.

Early studies in patients
Decisions on which dose and dose regimen to use for Phase 2a and 2b clinical trials may be facilitated by simulations that are derived from data collected from clinical trials in small numbers of healthy volunteers or patients. Such work seeks to understand the relationship between drug dose, pharmacokinetic profile and drug response and simulate potential treatment scenarios.[12] Figure 3a shows the relationships between an anticoagulant drug (the direct Factor Xa inhibitor TAK-442) and two parameters that are used to measure blood coagulation and drug concentrations. By describing these relationships in a mathematical model, the effect of different doses of drug and drug regimens may be simulated (Figure 3b).[13] Such simulations were used to inform the dose and regimen for the subsequent Phase 2 trials. In addition, simulations can facilitate selection of the optimum dose to balance benefit and risk before testing in larger patient populations.[14 15]

Drug-drug interaction studies
PBPK methodologies can also simulate drug–drug interactions and so provide important information[16 2] on which drug–drug interaction clinical trials should be conducted, the design of individual trials and their optimal timing.[17] An example of the output of simulations for the effect of the antifungal drug ketoconazole on the pharmacokinetic profile of a test drug is given in Figure 1b. This shows that ketoconazole, a known CYP3A4 inhibitor, increased the plasma concentration of the test drug. The information from such simulations assists in the design of the drug-drug interaction clinical trial, as well as helping to set the timing of the trial in the development schedule.

Special patient population studies
The assessment of drug clearance in special patient populations, such as the renally impaired, hepatically-impaired, children, the elderly and specific ethnic groups, is a substantial component of a clinical pharmacology programme. Indeed PBPK approaches can assist in the design of these clinical trials and assess the likely impact of features of these special patient populations on drug clearance.[18-20]

As confidence in PBPK models grows, and since this simulation approach can enable simulations of difficult to study combined effects of extrinsic and intrinsic factors on drug disposition, regulators have expressed interest in the utility of PBPK models as part of their review process[11 19 21] as well as in possible contribution to drug labels.

The simulation in Figure 1c shows that as hepatic impairment increases, the clearance of the drug decreases, suggesting that the administered dose may need to be decreased in this patient population. The information gained from the simulation can be used to aid the design of hepatic impairment studies and help to maintain the safety of patients with different degrees of hepatic impairment in other studies.

A simulation of the adjustment in drug dosage needed in paediatric patients, depending on their age, to achieve a target average concentration of free drug is provided in Figure 1d. As well as selecting an appropriate dose, such simulations facilitate the design of trials in terms of blood sample collection, which is of critical importance when conducting trials in children.

Formulation development
During the development of new drug formulations (such as extended release formulations), models that describe the relationships between drug dissolution profiles in vitro and pharmacokinetic profiles in vivo allow the simulation of human pharmacokinetics. Because these models use dissolution data obtained in vitro,[22 23] they circumvent the need for costly and time consuming in vivo bioavailability studies and so allow rapid progress in formulation development.

Physiologically based mechanistic models may also have utility in simulating formulation-food interactions.[24]

Proof of Concept

Clinical Proof of Concept (PoC) is a key decision making point in the drug development process. Initial proof that the concept may be efficacious in a clinical setting is obviously a key trigger point for major investment and a decision that the sponsor needs to take with some confidence that this will be supported by future, clinical trials. To be of value PoC, therefore, requires a definitive outcome. Simulations can help achieve this goal by feeding information on the known and assumed biology into many aspects of the design of PoC clinical trials (such as the inclusion and exclusion criteria, biomarkers and clinical endpoints) to ensure PoC studies are fully optimised.[25-28]

Three critical questions need to be addressed in the PoC clinical trial:

1. How much drug needs to be delivered to the target and for how long? This is largely a question that relates to pharmacokinetic properties of the drug and how it is delivered. The selection of an appropriate target patient population is based on the intended biology of the target. Pharmacokinetic–pharmacodynamic simulation can influence the design of the clinical study (eg. by defining inclusion and exclusion criteria, the sample size, biochemical and clinical endpoints and so on).[27 28] The model used for performing the simulation should be consistent with the mode of action of the molecule and translated to the clinical setting with appropriate scaling from in vitro, pre-clinical and clinical pharmacology study data.

2. How to determine if the drug is achieving the desired pharmacological activity (so called proof of mechanism) and clinical activity (that is, proof of concept)? The use of appropriate biomarkers of pharmacological activity, surrogate endpoints and clinical endpoints have a crucial role in determining proof of mechanism and PoC. The actions of the molecule and the target population can be tested in a simulation, allowing assumptions to be tested against the known biology. Such hypothesis testing leads to more robust design of clinical studies. Uncertainties in the model used to conduct the simulation can also be explored and managed. Gaps in understanding of the model will undoubtedly be identified during the process of exploring different scenarios as part of the simulation. However, this should be viewed as an opportunity to design the clinical trial to collect missing information.

3. Which patients will respond to treatment? Increasingly, stratified medicine approaches are being adopted very early in development to identify those patients who will achieve the most benefit from a given therapy, thereby avoiding the patients who will not gain from exposure to the drug. An example could be the ability of a specific antibody to reduce the levels of IgE in patients with a high production of IgE.[29]

An example of a pharmacokinetic–pharmacodynamic approach is illustrated in Figure 4 for a biotherapeutic monoclonal antibody against a soluble ligand. The accumulation of inactive monoclonal antibody-ligand complex often provides a good biomarker of target suppression for a soluble ligand even though this not measured directly (total ligand rather than free ligand concentration is measured in both the pre-clinical studies and the intended clinical trial). The concept of duration and extent of ligand suppression was simulated using a pharmacokinetic–pharmacodynamic model, which can then be tested in the clinic using an appropriate biomarker (the increase in total ligand concentration). At this stage of development there is no evidence of translation to a clinical benefit unless target suppression has already been validated as a surrogate endpoint. Nevertheless, the chosen trial design should confirm the desired pharmacology and allow appropriate dose and dosage regimens to be tested which optimise the ability to make this transition.

Dose ranging studies

The purpose of dose ranging studies is to characterise the relative safety and efficacy profile of a drug over a range of doses in order to define a clinically relevant dose, or range of doses.

It is difficult to conduct dose ranging studies, and decisions related to dose selection in clinical trials continue to be one of the major stumbling blocks in drug development. Key issues are the variability in clinical endpoints and/or difficulty in their capture and assessment, and problems associated with the methodology used to analyse the dose response relationship.[30]

The conventional approach to conducting dose ranging clinical trials attempts to identify doses that produce a clinical response that is statistically different to a given reference point (often the response produced by placebo). Usually, the lowest dose that produces a response that is significantly different to placebo is considered the minimum effective dose. However, this simple approach cannot quantify differences between active doses in a reliable manner or provide a quantitative estimate of the dose-response relationship; it can only detect its presence.[30]

Bornkamp, et al (2007)[31] state that the quantification of a graded dose response relationship requires a model based approach. All model based approaches assume that the observed response changes in a systematic manner with dose. This relationship is represented in a mathematical form which provides a graded, quantitative view of the underlying dose response relationship. Key to the success is that the mathematical form used reflects this relationship correctly. It is the pooling of simulated response data across all dose levels of a drug that allows model-based approaches to give more precise dose discrimination than conventional methods.

Experience has shown that functions which increase to a plateau describe the dose-response for most reversible pharmacological responses driven by a single receptor system. Bronchodilation caused by Đ-agonists or anti-muscarinics are examples of such systems. Figure 5 presents available spirometric results of nine randomly selected clinical trials and 10,000 simulated trials (100 patients per arm) in the presence of a steady-state antimuscarinic bronchodilator. The point-estimates (that is, a single value estimate of patient response) of the actual clinical trial data (red points), one for each dose arm, indicate that there are considerable differences from trial to trial; this is representative of the variability seen across different clinical trials. In contrast, the simulated curves vary much less from trial to trial because the simulation model integrates data obtained from all doses in each simulated trial providing a better estimate of the patient response at any given dose than can be achieved through the use of single point estimates.

Basing a decision of what doses of drug to use in a clinical trial on point estimates can lead to different doses being selected in different clinical trials, and it can then become difficult to select what the clinically relevant dose is. This is particularly true if the intention is to select a dose which is on the threshold of the plateau of the hyperbolic curve that defines patient response, which is commonly considered the optimal point for dose selection.

Confirmatory studies

Confirmatory Phase 3 clinical trials are the main source of data that support submissions for approval by regulatory authorities worldwide. Late-stage failure is a known hazard of drug development.[32][33] However whether a drug succeeds or fails can be influenced by the way the Phase 3 clinical trial is designed and conducted. Regulatory authorities recognise the value of clinical trial simulation in late stage development and both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) have released guidelines encouraging sponsors to use simulations wherever possible to improve the chance of success.[3-7] However, despite an extensive literature search we could not find any published examples of the value of entire clinical trial simulation in Phase 3 and this is a key barrier to its more widespread adoption.

The primary goal of clinical trial simulation in confirmatory studies is to produce simulated clinical data that allows researchers to optimise the design of the clinical trial and ensure that the proposed statistical analyses are valid and robust to the many operational challenges – such as those discussed below – that are inherent to Phase 3 trials.

Compared to Phase 2 clinical trials, Phase 3 trials include a larger and more varied patient population, multiple geographic regions, longer duration of treatment and more demanding clinical endpoints (such as multiple correlated endpoints and the presence of subgroup treatment effects). Simulation of these additional Phase 3 complexities, incorporating all available evidence that has been collected up to end of Phase 2, can help to optimise the design of Phase 3 clinical trials.

Patient recruitment can be simulated to improve the accuracy of predicting patient enrolment.[34] In the hypothetical example shown in Figure 6, using data from a real completed study, preliminary data suggest that simulation of recruitment estimates during a trial using emerging recruitment information increased the accuracy of the simulation and improved recruitment estimates. Moreover, simulation that takes place while the clinical trial is in progress can help researchers respond to operational challenges during the study, such as projecting the effect of unanticipated patient dropout.

Furthermore, clinical trial simulation may hold promise in clinical trials that use an adaptive design, accumulating data to modify certain future aspects of the study without undermining the validity and integrity of the trial),[35][31] in particularly with regards to the timing of the interim analysis.

Finally, drug supply requirements can be simulated using a model that accounts for the proposed randomisation structure and drug supply strategy. However, simulation is not routinely performed for drug supply planning and so opportunities for optimisation are being missed.

Concluding thoughts

We believe that clinical trial simulation will play an increasing role both for internal decision making within a company and in supporting applications for regulatory approval. The discipline of describing the known biology for a new drug in a mathematical model provides a tool which can bring all the knowledge of the molecule into one place. Components of the mathematical model that describe the biological system, which either cannot be measured or are not well understood, are clearly identified in a way which is very transparent and aids decision making. The ability to test assumptions of the biological and therapeutic effects of an investigational drug prior to the design of an experimental clinical trial should lead to clinical trials that have a greater probability of success. This is now widely recognised by industry and regulators. As simulations become increasingly adopted, their positive impact on the drug development process will become more evident and we recommend this is further characterised to drive their use and improve the efficiency of medicine development.

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Competing interests statement

The authors declare no competing financial interests.

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Figures

Figure 1: Examples of physiologically-based pharmacokinetic (PBPK) modelling
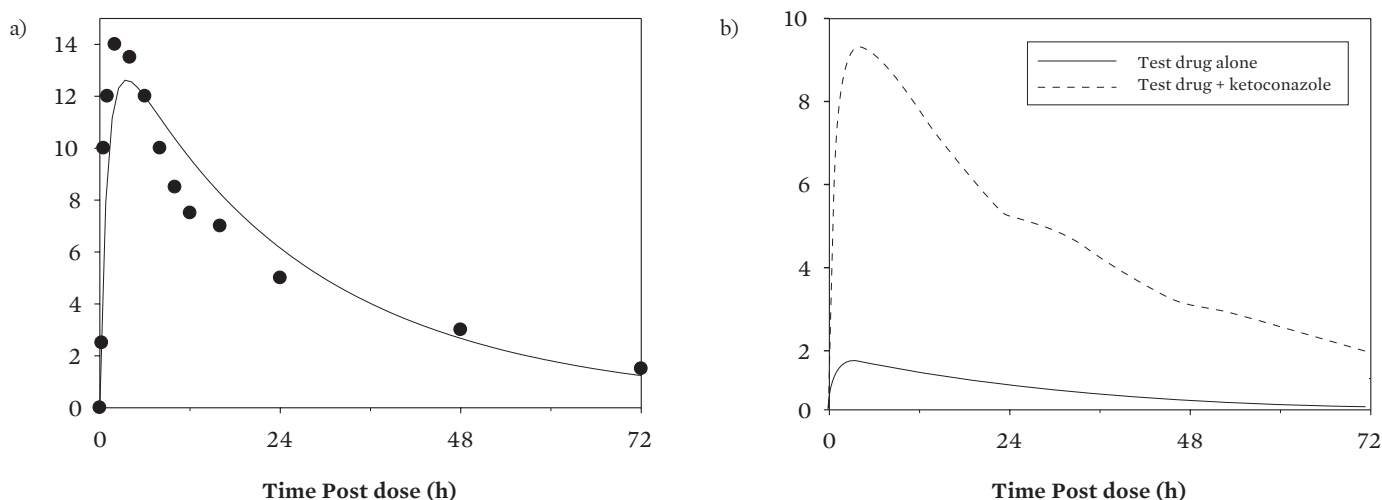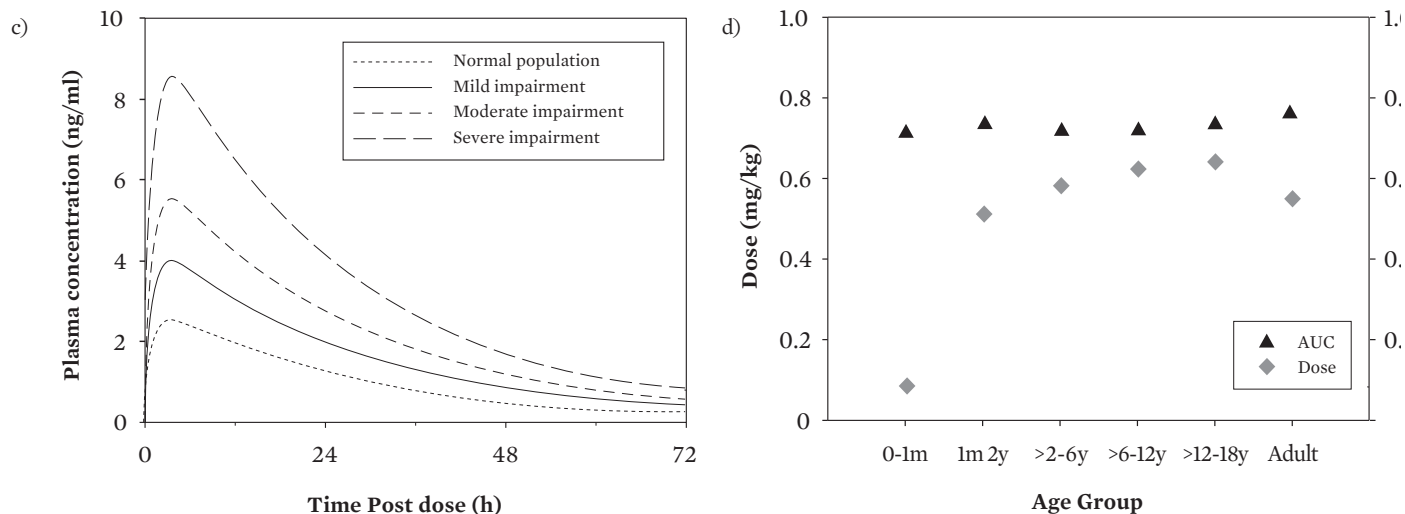
a) PBPK simulation of human plasma concentration time curve (solid line) overlaid with actual data (solid circles) showing how closely the actual data and simulated data were in this clinical trial.

b) Simulation of the effect of ketoconazole, an inhibitor of CYP3A4, on the pharmacokinetics of a test drug. This simulation is based on studies in vitro of the enzyme kinetics of the test drug. Different trial scenarios may be simulated using different doses and regimen of the inhibitor/perpetrator.

c) Assessing drug clearance in special populations. Simulation of pharmacokinetics of test drug following oral administration to normal healthy subjects and patients with mild, moderate and severe hepatic impairment, based on a PBPK model.

d) Setting appropriate doses for children. Simulation of required doses to achieve a target AUC in various age groups.
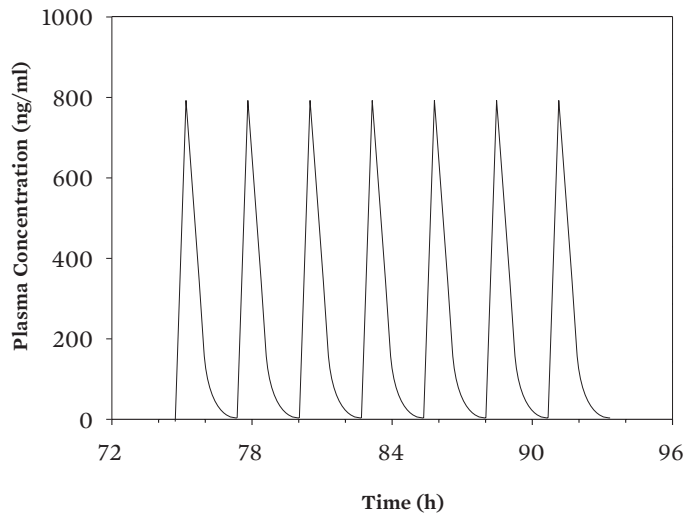
Abbreviations:
AUC – area under the plasma concentration curve
**CYP3A4** – cytochrome P450 3A4
**PBPK** – physiologically-based pharmacokinetic models.

Figure 2: Simulated plasma concentration-time profile of twice daily multiple dosing based on single dose data

Simulation of the pharmacokinetics of a drug after multiple dose administration based on knowledge of single dose pharmacokinetics – this sort of simulation can assist in setting the right dose and dose regimen to achieve a target plasma exposure and time course of concentration. These models are generally of the 'top down' variety as they describe the time course of the drug in plasma without detailed knowledge of the underlying physiological and biochemical processes that contribute to the drug's disposition.

**Figure 3: Dose/PK/drug response relationships and simulation of potential treatment scenarios**
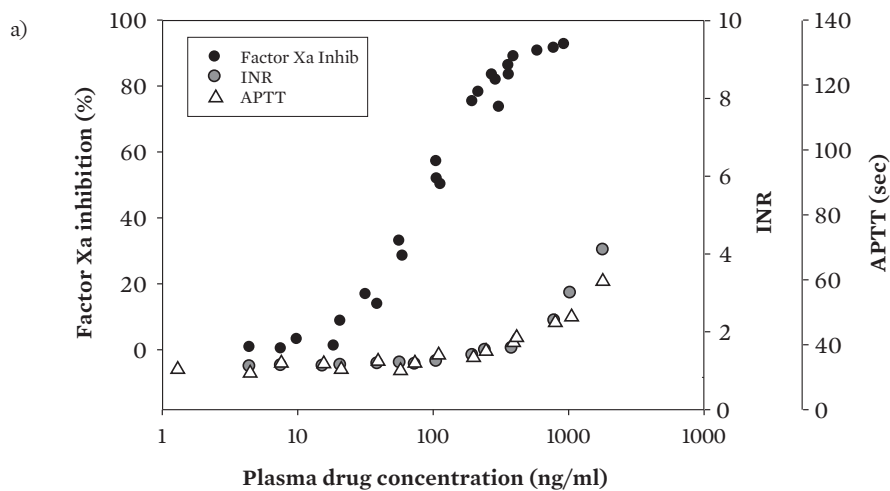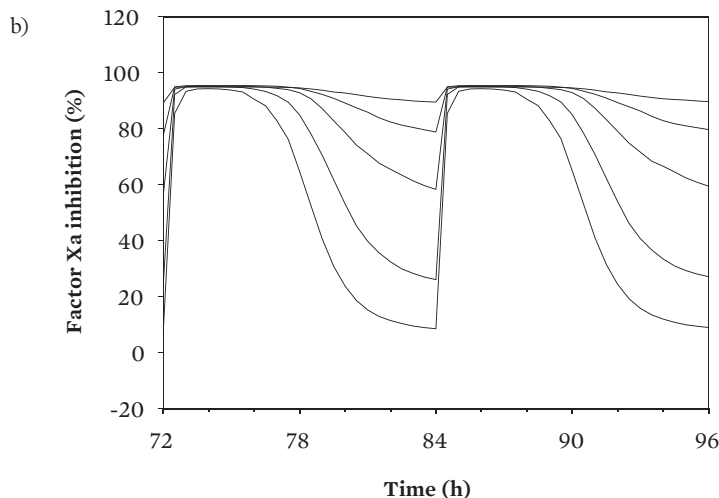
a) Relationship between pharmacodynamic parameters of Factor Xa inhibition/INR/APTT and plasma drug concentrations.

b) Simulation of effect of different TAK-442 doses on Factor Xa inhibition at steady state.

Abbreviations:
APTT - activated partial thromboplasin time
**INR** - international normalised ratio.

Figure 4: Simulation of target ligand suppression in the first-in-human study for a biotherapeutic monoclonal antibody against a soluble ligand
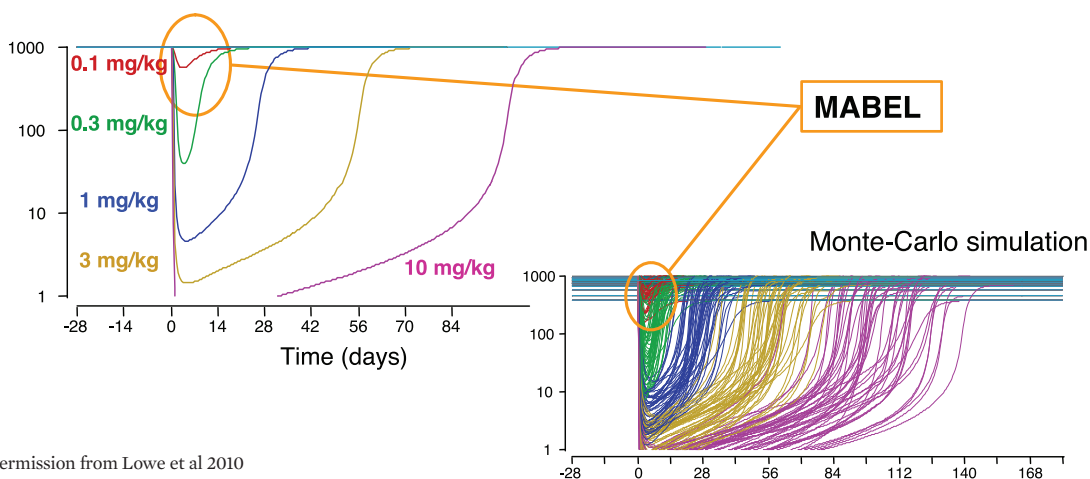
Reproduced with permission from Lowe et al 2010

Pre-clinical data showing the capture and accumulation of inactive antibody-ligand complex, antibody kinetics and target binding affinity were scaled from cynomolgus monkey to man. The proposed clinical doses were chosen to achieve an appropriate level of target suppression, with the starting dose giving a Minimal Acceptable Biological Effect Level (MABEL) for the first dose in humans. Monte-Carlo simulations of this trial design, incorporating known variability in the model parameters, shows that the chosen doses should be clearly separated in terms of duration of suppression of the target ligand.

Figure 5: More accurate dose selection. Nine simulated trials analysed by conventional and model-based approach (N=100 patients/arm)
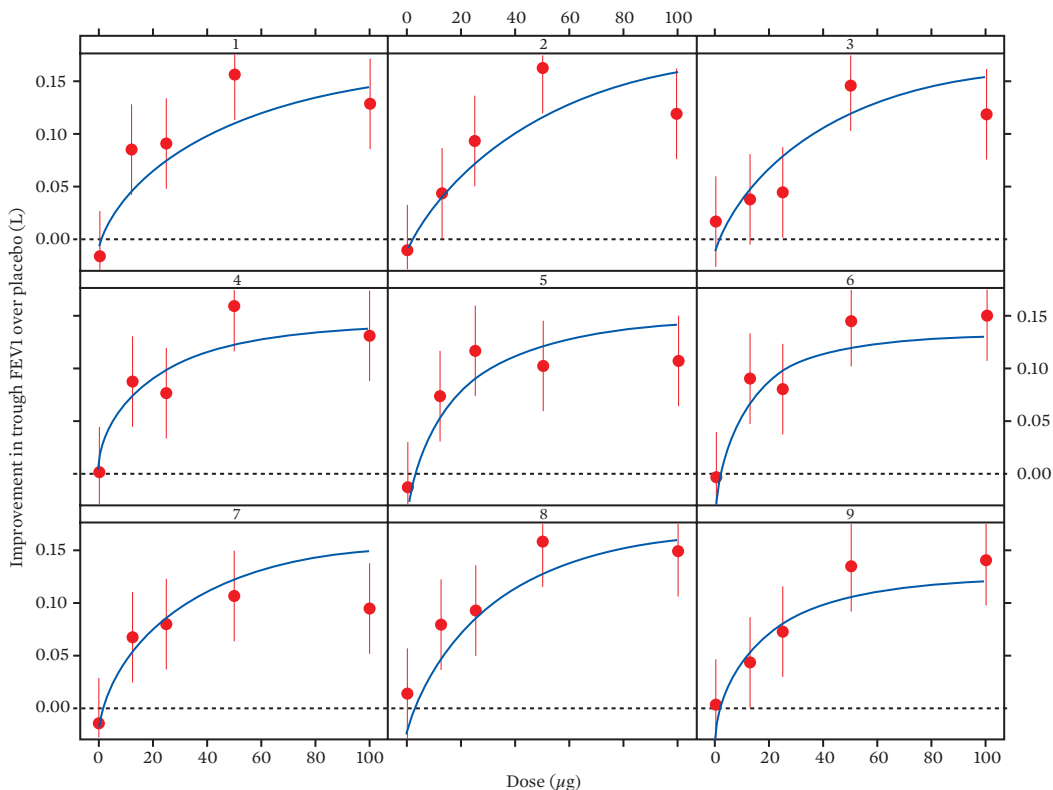

A total of 10,000 parallel group trials were simulated (blue lines), based upon data obtained from previous studies. The typical FEV1 dose response in these lung disease trials was assumed to have an ED50 of 15.2 ×g and an Emax of 177 mL. Noise was added by assuming a standard deviation of 225 mL. The dose levels considered were placebo, 12.5, 25, 50 and 100 ×g with 30, 100, or 300 patients in each study arm. The red points represent point estimates from nine randomly selected simulated trials (100 patients per arm).

Abbreviations:
ED50 – dose of study drug that is effective 50% of the time
Emax – maximum possible effect of the study drug
FEV1 – forced expiratory volume in 1 second.

Figure 6: Iterative data collection for more robust results. Combined plot of predicted versus actual recruitment in a Phase 3 confirmatory study

All predictions after 1st, 2nd and 3rd periods
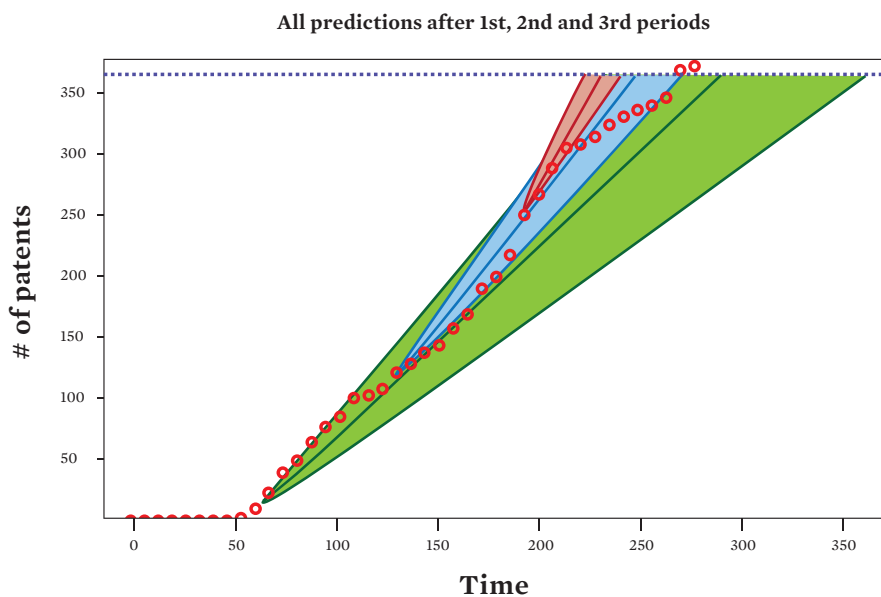
This is an example of a retrospective analysis of a real completed study, with the target number of patients represented by the blue dotted line. The recruitment duration was divided into three equal periods, before which recruitment estimates were revised as denoted by the different colour shaded areas on the plot. As the number of patients increases the simulation becomes more accurate, and there is increased overlap with the actual recruitment data (red circles), showing that simulations can help predict recruitment rates. To make the simulation even more accurate, it would be necessary to adjust recruitment rates on an ongoing basis as new information becomes available.

Source: Anisimov 2009