Quantitative Systems Pharmacology Models: Potential Tools for Advancing Drug Development for Rare Diseases

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Rare diseases, affecting millions globally, present significant drug development challenges. This is due to the limited patient populations and the unique pathophysiology of these diseases, which can make traditional clinical trial designs unfeasible. Quantitative Systems Pharmacology (QSP) models offer a promising approach to expedite drug development, particularly in rare diseases. QSP models provide a mechanistic representation of the disease and drug response in virtual patients that can complement routinely applied empirical modeling and simulation approaches. QSP models can generate digital twins of actual patients and mechanistically simulate the disease progression of rare diseases, accounting for phenotypic heterogeneity. QSP models can also support drug development in various drug modalities, such as gene therapy. Impactful QSP models case studies are presented here to illustrate their value in supporting various aspects of drug development in rare indications. As these QSP model applications continue to mature, there is a growing possibility that they could be more widely integrated into routine drug development steps. This integration could provide a robust framework for addressing some of the inherent challenges in rare disease drug development.

ADDRESSING THE UNMET MEDICAL NEED FOR RARE DISEASES

Rare diseases are defined as conditions that affect fewer than 200,000 patients in the United States, while in the European Union, a disease is considered rare if it occurs in less than 1 in 2,000 individuals.[1,2] These diseases typically manifest as chronic and sometimes life-threatening conditions, predominantly diagnosed during childhood. There are approximately 7,000 rare diseases collectively, with a global prevalence estimated to exceed 300 million people. In the United States, rare diseases are estimated to affect approximately 15.5 million individuals, with healthcare expenses amounting to USD$ 997 billion per year.[3] Despite this, over 90% of these conditions lack approved treatments, highlighting the significant unmet need.[4] This scarcity of therapeutic options is particularly alarming, considering that these treatments could potentially be lifesaving for those affected by these diseases.

The development of treatments for rare indications often present unique challenges, resulting in difficulty in executing randomized, double-blind, placebo-controlled studies, the gold standard in drug development. Rare indications are characterized by limited patient numbers that are often geographically dispersed, complicating the recruitment and logistics of traditionally designed clinical trials.[5,6] This results in low patient recruitment numbers with lengthy recruitment periods, which can lead to underpowered clinical studies.[7] Rare indications also present with high phenotypic heterogeneity and variable disease progression that can lead to significant variations in drug response from patient to patient, and this compounded with low patient numbers can often make the outcomes of clinical trials difficult to interpret.[8–12] All these factors can make it challenging to meet the regulatory requirements for drug approval.

Regulatory agencies have taken proactive steps in an effort to streamline the process of drug development, particularly for rare indications. They have established a set of recommendations and conducted workshops to clarify their stance and aid sponsors. One of the key recommendations put forth by these agencies is the adoption of Model-Informed Drug Development (MIDD). This approach has been endorsed by several regulatory bodies, including the European Medicines Agency (EMA) in 2006 and the Food and Drug Administration (FDA) in 2014, 2017, and 2019a, as well as the FDA and M-CERSI in 2023. MIDD is a strategic tool that can significantly enhance the various stages of drug development by facilitating data-driven decision-making, optimizing the design of clinical trials, and de-risking uncertainties.[13–15] Moreover, MIDD approaches have the potential to make a substantial contribution to the body of evidence presented to regulatory agencies by providing comprehensive data and insights that strengthen the case for drug approvals.[16,17] The application of MIDD in rare drug development has the potential to optimize the drug development process, thereby benefiting both the sponsors and the patients who await these critical treatments.

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QSP IN DRUG DEVELOPMENT

Pharmacometric approaches are established tools widely applied in various stages of drug development. These approaches provide predictive analysis of pharmacokinetics and pharmacodynamics and are used to understand the dose–response relationship in preclinical studies to derive a safe dose for first-in-human studies. These approaches also contribute to the analysis of phase I/II data to optimize the dose for safety and efficacy in phase III trials.

Quantitative Systems Pharmacology (QSP) models are emerging as promising tools to support many aspects of drug development, particularly in the context of rare diseases.[18] QSP models incorporate mathematical representations of key pathophysiological processes in a disease of interest, spanning multiple scales of biology from signaling pathway dysregulation to organ-level dysfunction.[19–21] They link the mechanism of action (MoA) of a drug to the appropriate biological reactions at the sub-cellular scale, integrating the properties of a drug candidate with current available data on the disease etiology, target expression, and relevant physiological processes and variability.[22] By doing so, these models can describe the dynamic relationship between a drug and its target to gain insight into the therapeutic response at the sub-cellular, cellular, and in some cases organ level (**Figure 1**).

QSP, while relatively new, complements other established modeling and simulation approaches widely used to analyze data from preclinical and clinical studies of a drug candidate.[20,21] Unlike pharmacometric approaches, which mathematically describe drug exposure and the trajectories of biomarkers and clinical end points from a defined dataset without considering a biological mechanism, QSP models offer an interpretable framework for understanding and predicting disease progression and therapeutic response. These models integrate diverse data sources, extending beyond the traditional datasets collected during clinical drug development, incorporating prior knowledge already available in the public domain to add context to the clinical data derived from the drug candidate. Prior knowledge includes information on physiology, biochemistry, and pharmacology and can be combined with relevant preclinical and clinical datasets to inform key features of the disease and drug response to be represented in the model. Natural history datasets and clinical datasets from other drugs with the same indication can also be incorporated into the modeling effort, allowing quantitative comparisons of efficacy. By accounting for all these data sets and the current understanding of the pathophysiology and the pharmacology of the drug, an integrative view of the disease and possible response in virtual patients is formed. In addition, evaluating all these data sources during model development and attempting to combine them into a cohesive mathematical representation of the observed pathophysiology and response can be tremendously helpful and can result in the identification of knowledge gaps that need further experimentation.

QSP MODELS APPLIED IN DRUG DEVELOPMENT IN RARE DISEASES

The value of the QSP approach lies in its ability to connect drug-target engagement to biomarkers and clinical end points in a mechanistic manner, providing a representation of the disease and drug response in virtual patients. The bottom-up nature of QSP models allows the simulation of untreated and treated virtual patients to support various aspects of drug development starting in discovery and extending through late development.[19] These model applications include drug target and drug candidate prioritization, translating preclinical efficacy to predict first-in-human dose in the target patient population, biomarker justification, dose optimization, exploration of different dosing regimens, and efficacy predictions in patient

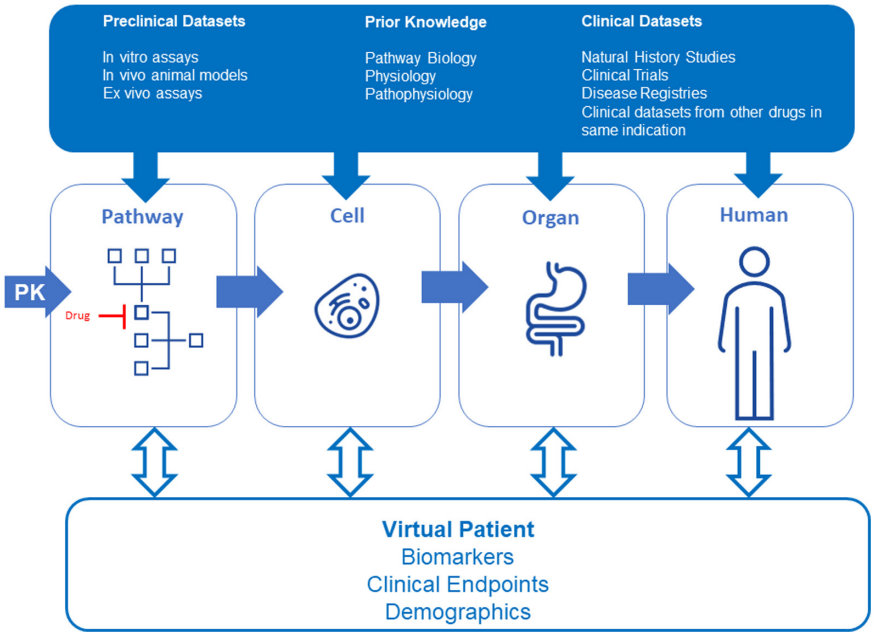

Figure 1 Overview of QSP approach. QSP models describe pathophysiology and pharmacology at different biological scales informed by data from various sources to describe biomarkers and clinical end points in virtual patients.

subpopulations considering age, disease burden, and other factors that may affect the exposure–response relationship. The following QSP model case studies illustrate some of these applications and how they impact many stages of drug development in rare indications.

Application: translating preclinical data to predict first-in-human dose

QSP models can support first-in-human dosing for rare indications by incorporating mechanistic knowledge on the pathophysiology targeted and integrating it with the preclinical evidence accumulated from early discovery. The translation of preclinical efficacy by QSP models can extend beyond the information obtained from the customary animal disease models that may not adequately recapitulate the key features of the disease of interest. QSP models can complement conventional approaches that rely on allometric scaling and safety thresholds obtained from preclinical studies to predict therapeutic doses in the intended patient population. The QSP approach can also be applied to justify the efficacious dose in phase II trials, particularly when the phase I trial was performed in healthy volunteers. The following case studies illustrate examples of QSP approaches applied to support target justification and dosing predictions in rare indications.

Case Study 1: Preclinical translation of brain exposure:response. The QSP analysis by Jafarnejad *et al.* demonstrates the usefulness of applying QSP-based preclinical translation to inform the first-in-human dosing in a rare indication patient population.[23] The QSP model focused on Mucopolysaccharidosis type II (MPS II; ORPHA:580), a disease caused by mutations in the iduronate-2-sulfatase (IDS) gene. IDS is an enzyme responsible for the lysosomal degradation of glycosaminoglycans (GAGs). IDS deficiency leads to the accumulation of GAGs and results in complex clinical phenotypes involving multi-organ dysfunction, including hepatosplenomegaly, hearing loss, and cardiac valve disease.[24] In the severe clinical phenotypes, affecting about two-thirds of the patients, the brain is also impacted, resulting in cognitive deficits. Standard of care is enzyme replacement therapy (ERT) consisting of weekly intravenous (IV) infusions of recombinant IDS. However, IV IDS ERT is unable to reduce GAGs accumulation in the brain due to its limited ability to cross the blood–brain barrier. A novel IV-administered fusion protein (ETV-IDS) utilizes transferrin receptor (TfR)-mediated transcytosis to improve brain uptake.[25] A QSP model of the GAG dynamics in the brain and CSF was developed. In this analysis, simulated ETV-IDS treatment was evaluated against those from other ERT types with various modes of administration, with the goal of ranking these drugs based on improved brain exposure. The model was informed by preclinical brain and CSF pharmacokinetics and pharmacodynamics for each ERT type, and then applied to assess the relationship between biodistribution and efficacious GAG reductions in brain and CSF for ERT types with varying brain penetration capabilities.[23] Based on the factors affecting the exposure:response relationship, the efficacious dose for ETV-IDS was predicted for MPS II patients. A phase II/III clinical trial is currently ongoing (NCT05371613).

Case Study 2: Understanding drug–multitarget interaction to propose efficacious dose. The next case study applies a QSP model to predict the efficacious dose for a recombinant protein for the treatment of Duchenne Muscular Dystrophy (DMD; ORPHA:98896).[26] DMD is a rare neuromuscular disease caused by the absence of dystrophin, which leads to progressive muscle degeneration and weakness, causing loss of ambulation and eventual death due to respiratory and cardiac failure. Minimizing muscle wasting and enhancing muscle mass/strength are promising DMD treatment strategies currently being pursued. Follistatin, an endogenous circulating glycoprotein, is a candidate therapeutic for DMD as it promotes generation of muscle tissues by preventing known mediators of muscle wasting, myostatin and activin, from binding to their receptor activin type IIB (ActRIIB). FS-EEE-Fc, an investigational DMD drug, is an engineered recombinant protein form of follistatin. The DMD QSP model described both myostatin and activin dynamics, and their interaction with ActRIIB. The model also described how myostatin and activin binding to ActRIIB leads to inhibition of muscle growth in DMD. Simulations of FS-EEE-Fc treatment showed efficacy against muscle wasting, and this response was further characterized by simulating the muscle wasting effect when FS-EEE-Fc solely targeted myostatin or activin. The model indicates that inhibiting both myostatin and activin pathways simultaneously enhances muscle growth more effectively than targeting myostatin alone, thereby supporting the rationale for the dual-targeting design of FS-EEE-Fc. The model was applied as a translational tool to understand the degree of dual pathway inhibition of activin and myostatin needed to have meaningful muscle growth. Based on analysis of recent DMD clinical trials, an efficacy threshold of 7% muscle mass growth was deemed clinically meaningful in functional muscle metrics. Using this threshold, a potential efficacious dose was proposed that would result in >7% muscle mass.

Application: gaining insight into complex biology

The coagulation cascade has been a popular topic in several systems biology and QSP models (reviewed here[27]). The coagulation cascade involves a network of binding interactions between coagulation factors and proteolysis events, with multiple feedback loops leading to thrombin generation and eventual fibrin changes. The highly complex and nonlinear nature of the coagulation cascade benefits from mechanistic modeling, as without it, intuitive understanding is challenging if not impossible.[28] QSP models can account for this complexity by simulating the key biochemical interactions and feedback regulations, which have been extensively characterized, providing a mechanistic understanding of the factors impacting clotting events and the drugs that modulate them. This modeling approach benefits from the availability of quantitative measures related to coagulation, such as physiological levels of coagulation factors in healthy or disease states, and *in vitro* assays routinely used in the clinic to quantify clotting function in individuals. These

measurements allow for parameter estimation and validation, enhancing the model's quality and performance to support clinical drug development. Several QSP models have been applied to simulate the effects of various therapies (both established and novel) on the coagulation cascade under different clinical scenarios, with the goal of gaining insight on drug responses, and optimizing treatment strategies.

Several rare diseases are associated with clinical bleeding, including inherited deficiencies of coagulation factors such as hemophilia A and B (involving deficiencies in factors VIII and IX, respectively; ORPHA:448). These diseases are often treated with factor supplementation, as well as other emerging non-factor modalities. Several QSP models of hemophilia A and B have been developed by leveraging existing models of the coagulation cascade in the healthy state and reducing factor VIII or factor IX, respectively, as exemplified in ref. [29–33]. The following two case studies showcase QSP models that have been applied to assess the impact of different coagulation factors and interventions on thrombin generation dynamics and have represented drug effects in terms of clinically relevant metrics of coagulation.

Case Study 3: Mechanistic insight into clinical metrics of coagulation. Nayak *et al*. developed a QSP model of hemophilia A that contained descriptions of some of the standard *in vitro* assays used to monitor the coagulation potential of a patient, such as the thrombin generation assay (TGA). This model was applied to mechanistically understand the readouts of these assays and assess the clotting potential of the intrinsic and extrinsic pathway of the coagulation cascade.[29] The model, informed by data from healthy or hemophilia plasma, evaluated the effects of modulating different coagulation factor levels (active and inactive), identifying which of the coagulation factors may contribute most to variability in response to factor supplementation treatment in hemophilia A. This study quantified the diverse effects of each factor on the outputs of these *in vitro* assays, accounting on their placement within the coagulation cascade. This type of insight could support a mechanistic interpretation of unexpected assay readouts in a clinical setting, and start to understand how the naturally occurring variability in coagulation factor expression (other than factor VIII or factor IX) may lead to variability in treatment effect.

Case Study 4: QSP-based assessment of hemostatic equivalency between a new drug and standard of care. Mechanistic modeling has also been applied to innovative non-factor approaches of treating hemophilia. A model for GalNAc-conjugated siRNA was developed using published data for fitusiran, an investigational siRNA therapeutic that targets antithrombin (AT) to rebalance hemostasis in hemophilia A or B. Fitusiran treatment has been shown to significantly reduce bleeding events compared to factor supplementation.[34,35]

To gain insight into the hemostatic equivalency of fitusiran prophylaxis (i.e., AT lowering) compared to conventional factor supplementation, a QSP model was developed to represent the thrombin generation in hemophilia A upon AT lowering, considering the effect of alpha-2-macroglobulin, another key thrombin modulator.[36] The QSP model represented the *in vivo* dynamics of the coagulation factors resulting in thrombin generation and included descriptions of *in vitro* coagulation assays, such as the TGA. A virtual population (VP) of untreated severe hemophilia A patients was generated and used to simulate TGA metrics. These simulated TGA metrics were compared to observed clinical data to establish the validity of the VP and gain confidence in its applicability for the hemostatic equivalency analysis. Simulated TGA metrics from this VP with reduced AT levels were evaluated against simulated TGA metrics derived from the same VP but instead treated with supplemental factors. This VP analysis of fitusiran provided predictions of hemostatic equivalency with FVIII supplementation in a representative population of severe hemophilia A patients, allowing the in silico evaluation and comparison of two different treatment approaches in terms of thrombin generation dynamics. Given the mechanistic underpinning and the breadth of data incorporated for QSP model validation in both the healthy and disease states, such QSP approaches may also be leveraged to support drug development in ultra-rare bleeding disorders caused by deficient activity of other coagulation factors.[37]

Application: incorporating natural history and real-world data into QSP models

QSP models provide an integrated "systems level" approach to describe the interplay between disease and the MoA of a drug. These models are informed by data from various sources rather than a single clinical trial dataset, providing biological constraints to the physiological scales included in the model (**Figure 1**). These various datasets can include natural history studies and real-world data in the form of disease registries. Disease registries are observational data collections from patients diagnosed with a specific type of disease. For rare diseases, where clinical trials are often of small size and patients display high phenotypic variability, disease registries are valuable data sources to help understand disease progression and the degree of variability expected in the patient population.[38] The next two case studies highlight QSP models where natural history or registry datasets were incorporated to inform long-term efficacy predictions, or therapeutic response predictions in a more diverse or realistic patient population.

Case Study 5: Predicting long-term response from short-term observations informed by natural history data. The QSP model of vosoritide provides an example of leveraging natural history data to translate short-term observations of clinical efficacy into long-term clinical benefit. Vosoritide is a recently approved treatment for Achondroplasia (Ach; ORPHA:15), an autosomal dominant form of skeletal dysplasia resulting in short stature, with a worldwide incidence of 1/25,000. Ach is caused by mutations in the fibroblast growth factor receptor 3 (FGFR3), leading to its over-activation and resulting in reduced bone growth velocity due to dysregulation of the development growth plate. Vosoritide's MoA is the stimulation of the natriuretic peptide receptor 2 (NPR2) to downregulate the excessive FGFR3 signaling observed in Ach. A QSP model was developed to represent the contribution of healthy and excessive FGFR3 signaling on bone growth. By mechanistically describing FGFR3 and NPR2 dynamics and

their modulation of signaling in growth plates in the bone, the model connected FGFR3 activation levels to growth velocity and terminal height in either healthy individuals or in Ach patients.[39] The model leveraged longitudinal height data from the CDC in healthy individuals and natural history studies in Ach patients, as well as data from other rare indications impacting height due to dysfunction in the FGFR3-NPR2 pathway. The QSP model reproduced longitudinal height data for both healthy and Ach populations from infancy through adulthood by modulating the FGFR3-NPR2 pathway kinetics accordingly. The model also reproduced the effect of vosoritide treatment on growth velocity and predicted the impact of long-term treatment on terminal height. This type of QSP modeling exercise could be applied to compare the long-term benefit of drug candidates being developed in Ach, where terminal height would not be amenable to be evaluated during the duration of a traditional clinical trial.

Case Study 6: Accounting for phenotypic heterogeneity by incorporating real-world data. Gaucher disease (ORPHA:355) is caused by deficient activity of the lysosomal enzyme acid beta-glucosidase (GCase), due to mutations in the GBA gene. GCase is a key enzyme in the glycosphingolipid pathway as it degrades the glycosphingolipid glucosylceramide (GL-1) to ceramide. Progressive accumulation of GL-1 in many tissues leads to multi-systemic disease manifestations including massive splenomegaly and bone disease. The degree of enzyme deficiency of GCase gives rise to a spectrum of disease phenotypes, ranging from the non-neuronopathic type 1 (GD1) to the most severe type 2 (GD2) and intermediate type 3 (GD3), which are both characterized by neurological manifestations in addition to visceral symptoms. Patients with GD2 do not survive infancy.

Gaucher disease was the first lysosomal storage disease to be treated with ERT (imiglucerase, marketed as Cerezyme), where the patient's deficient endogenous GCase activity was supplemented with intravenously administered recombinant enzyme. Subsequently, the substrate reduction therapy (SRT) approach was developed for treatment of GD1 (eliglustat, marketed as Cerdelga). While ERT supplements enzymatic degradation of GL-1, SRT acts through inhibition of GL-1 synthesis via an orally administered small molecule.

A QSP modeling analysis was performed to provide mechanistic insight into SRT efficacy following a switch from ERT treatment in GD1 patients, a population in which a range of different mutations in GBA gene is associated with variable disease severity. For this purpose, this analysis leveraged the extensive real-world data collected by the International Collaborative Gaucher Group (ICGG) Gaucher Registry in addition to the preclinical, clinical data and natural history data typically incorporated into QSP models. The ICGG Gaucher Registry (NCT00358943), a Sanofi Genzyme-sponsored program first established in 1991, is the largest voluntary observational database for Gaucher disease.[40] The registry records demographics and clinical outcomes for more than 6,000 patients from over 50 countries, regardless of treatment history or status. All participants in the eliglustat clinical trials and the ICGG Gaucher Registry provided written informed consent allowing post hoc analysis of de-identified data.

Through incorporating the extensive genotype and clinical endpoint data collected by the ICGG Gaucher Registry, this analysis illustrated how real-world evidence can be incorporated into QSP models. This enables the development of QSP virtual populations that are more diverse than those often enrolled in clinical trials for rare indications, including appropriate representations of mild, moderate, and severe genotypes, and hence supports prediction of therapeutic effects in critical sub-populations.

Application: exploring new drug modalities

Mechanistic models can support new drug modalities, such as oligonucleotide therapeutics and gene therapies, where their pharmacology introduces PK and PD complexities due to the multi-step MoA of these new therapeutics. Oligonucleotide therapeutics, which include antisense oligonucleotides and siRNAs, show promising clinical outcomes for rare indications such as Duchenne muscular dystrophy, familial amyloid neuropathies, and macular degeneration.[41] However, understanding the exposure:response relationship of these therapeutics using conventional approaches is challenging. For instance, it is common to observe transient plasma exposures for siRNA but prolonged gene silencing that can last for weeks or months.[42] The limited clinical relevance of plasma PK (as a driver of PD at the tissue site of action) coupled with highly restricted accessibility of tissue biopsy sampling in humans pose additional hurdles to characterize the exposure:response relationship.[42] There have been several mechanistic models developed that have represented the key steps required for siRNA to gene silence such as cellular uptake, assembly of RNA-induced silencing complex (RISC), and degradation of mRNA leading to reduction in the expression of the target proteins.[43,44]

Gene therapy holds great promise for the treatment of rare diseases, many of which are currently deemed challenging to treat. By directly correcting the patient's genetic material, gene therapy has the potential to address the root cause of many of the monogenic rare diseases, rather than just addressing the symptoms, and can provide long-term benefit, and in some cases, a permanent cure. Gene therapies for several rare indications such as Spinal Muscular Atrophy, cerebral adrenoleukodystrophy, β-Thalassemia, hemophilia A/B, retinal dystrophy, and Duchenne Muscular Dystrophy have recently been FDA-approved.[45]

Gene therapy clinical trials have their own unique challenges.[46] Gene therapies involve the delivery of genetic material into the tissue of interest, which subsequently produce therapeutic proteins in a multi-step process to give rise to efficacious response. Usually only a single dose is administered per patient due to safety concerns. This leads to a complex relationship between the "dose" of a gene therapy, the concentration of the resulting transgene in the body, and its therapeutic effect. There is no conventional PK, making pharmacometric approaches that are traditionally performed during clinical development not applicable. Classic concepts that describe PK such as absorption, distribution, metabolism, and excretion are not relevant to describe the dynamics of viral or cellular therapies. In addition, gene therapy trials tend to recruit a limited number of patients presenting with high phenotypic heterogeneity, which may make the application of statistical approaches to interpret efficacy results challenging. Randomized placebo-controlled

trials for evaluating gene therapies may not be feasible, especially in rare diseases for which ethical considerations may be needed[47] due to factors such as high mortality and lack of alternative treatments.

These unique features and complexities indicate that the design of gene therapy trials would benefit from tailored modeling and simulation approaches that can represent the transgene expression and efficacy of gene therapy in a limited number of patients to understand the exposure:response relationship.[48] QSP models, given their mechanistic foundation, could provide such a framework to support gene therapy clinical development by representing the relevant biological processes that must be accounted for to describe the biodistribution of the transgene and efficacy of gene therapy. These approaches could be applied to inform dose predictions and clinical trial design of gene therapies. The following case studies describe QSP models that represent the complex steps involved in viral or cell-based gene therapy and the resulting efficacy in rare indications.

Case Study 7: QSP model of viral gene therapy to understand viral dose:efficacy relationship. A few QSP examples are available that incorporate mechanistic representations of the key processes for viral-based gene therapies of rare indications, including the viral vector distribution in the target tissue, transduction efficiency of these cells, transgene expression, and efficacy.[49,50] Rao *et al*.[50] developed a detailed model that described the relationship between viral dose and viral vector distribution to transgene expression and clinical efficacy of Fidanacogene elaparvovec (commercialized as Beqvez®), a recently approved gene therapy for treating hemophilia B. This model was calibrated based on published data on AAV8 vectors, pre-clinical studies of liver-targeted AAV8, and clinical data from the phase I/IIA clinical trial of Fidanacogene elaparvovec.[51] Simulated FIX activity was compared to observed data from the Fidanacogene elaparvovec clinical trial, with the simulations showing much faster time to FIX activity steady state than observed. The model was then used to explore hypotheses that would account for these discrepancies on the predicted onset of steady state FIX activity.

Case Study 8: QSP model of cell-based gene therapy and resulting efficacy. Cell-based gene therapy is an innovative technique that involves extracting cells from a patient, genetically modifying them *ex vivo* to correct or enhance their function, and then reintroducing them into the patient's body. These modified cells can target and combat specific diseases, offering a personalized and highly effective treatment option. Nevertheless, cell-based gene therapies also must contend with several complex steps required prior to dosing that may impact efficacy. A QSP model of cell-based gene therapy for sickle cell disease (SCD; ORPHA:232) illustrates this. SCD is caused by a mutation in the β-globin gene that produces abnormal structure hemoglobin (HbS), leading to HbS polymerization and red blood cell (RBC) sickling. This results in vaso-occlusive crises, anemia, and organ damage that can eventually lead to death. SAR445136 is a zinc finger nuclease *ex vivo* gene editing therapy that targets the erythroid specific enhancer region of the transcription factor *BCL11A*, to switch the expression to fetal hemoglobin (HbF). By expressing increased levels of HbF, SAR445136-edited cells exhibit reduced HbS polymerization which is expected to ameliorate RBC sickling and the SCD phenotype.

A QSP model was developed to account for steps in the manufacturing and delivery of cell-based therapy such as stem cell mobilization from the bone marrow, gene editing of stem cells and bone marrow ablation prior to modified stem cell reintroduction and engraftment, to gain insight into the factors that could influence the variability of clinical response observed in the phase I/II trial of SAR445136 (PRECIZN-1; NCT03653247).[36] The SCD QSP model included a realistic representation of erythropoiesis that describes hematopoietic stem and progenitor cells and erythroid progenitors in the bone marrow and the resulting cell progeny in the periphery in SCD patients. The SCD erythropoiesis model was adapted to describe the MoA of SAR445136 by representing the key steps of prior to dosing, such as bone marrow ablation followed by the introduction of modified CD34+ cells with enhanced HbF expression, and hematopoietic reconstitution that will eventually give rise to RBC with enhanced HbF expression in the patient. The QSP model was applied to explore the observed inter-patient response variability to SAR445136 treatment by assessing the effects of treatment parameters such as degree of stem cell mobilization, cellular dose, and engraftment variability. A systematic evaluation of how these treatment parameters could impact long-term HbF expression could provide a blueprint for improved efficacy, by suggesting minimum product characteristic thresholds for improved efficacy. The structure of the QSP model also enabled its use for comparative analysis of efficacy of other cell-based gene therapies for SCD using different modalities, including CTX001 (marketed as Casgevy®) which uses CRISPR and the lentiviral vector gene therapy lovotibeglogene autotemcel (marketed as Lyfgenia®). The model's ability to recapitulate these related therapies data provided further qualifying support for its application.

Application QSP-based digital twin analysis

One of the benefits of applying QSP approaches to clinical data is that it enables the generation of digital twins.[52,53] In the industrial sector a digital twin is used as an *in silico* replica of a physical object in order to optimize it through computer simulations (the authors consider the terms "digital twins" and "virtual twins" interchangeable when applied to QSP modeling, even though they are considered distinct concepts in other sectors such as industrial manufacturing). Similarly, QSP-derived digital twins are calibrations of the QSP model to each patient's set of data, using a small subset of the model parameters, to describe the patient's own PK, biomarker and clinical end-point profile along with their demographics (age, body weight, sex, etc.) (**Figure 2**). This results in each patient being represented using the same QSP model structure employing a subset of parameters that are personalized or patient specific. Digital twin generation allows for the accounting of the observed intrinsic variability in the disease presentation of each patient. Digital twins have enormous potential in drug development, especially when it comes to personalized medicine: they can be used to simulate individual therapies in advance and visualize potential efficacy and disease progression. By incorporating

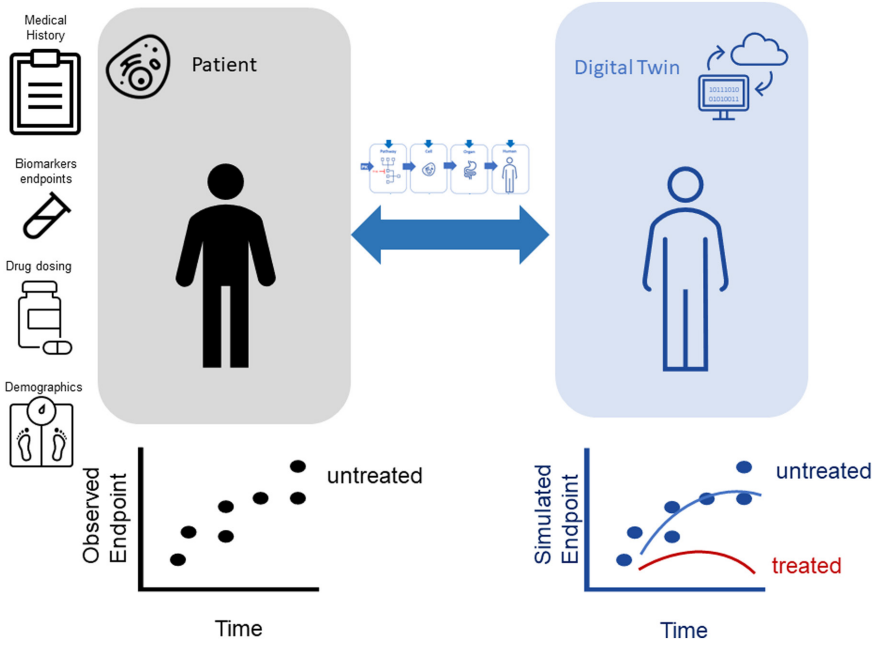

Figure 2 QSP-based digital twins are a model representation of the actual patient's biomarker and clinical end-point profile, considering the patient's disease presentation, relevant medical history, drug dosing regimen, and demographics. Digital twins can simulate disease progression or treatment response.

patient-specific data into these models, it may be possible to predict individual responses to drugs, thereby enabling the development of treatments that are tailored to the disease presentation of each patient.

Case Study 9: Digital twin-based analysis to account for disease heterogeneity in clinical trial baselines. Pompe disease (ORPHA:365) is a rare, progressive neuromuscular disease caused by deficient lysosomal glycogen degradation through the enzyme acid alpha-glucosidase (GAA). In the more severe infantile-onset (IOPD, ORPHA:308552) phenotype, patients experience symptom onset within the first months, or even days, of life. IOPD is characterized by cardiomyopathy in addition to skeletal and other multi-systemic manifestations. If untreated, IOPD is usually fatal in infancy.

Similar to other lysosomal storage diseases, both IOPD and late-onset Pompe disease (LOPD, ORPHA:420429) are treated through ERT, where the deficient endogenous enzyme is supplemented with recombinant human GAA (rhGAA) to break down accumulated tissue glycogen. Alglucosidase alfa (commercialized as Myozyme or Lumizyme) is the first ERT developed for Pompe disease. Avalglucosidase alfa (commercialized as Nexviazyme or Nexviadyme) is the next generation rhGAA, glycoengineered to have improved targeted cellular uptake.

Due to small patient numbers in IOPD and the high phenotypic heterogeneity observed in this population, the comparison of clinically observed treatment response is complex. To address this challenge, a QSP-based digital twin approach was applied to perform an *in silico* comparison of the efficacy of avalglucosidase alfa and alglucosidase alfa in IOPD patients.[54] A QSP model was developed that represents key elements of Pompe disease pathophysiology across the phenotypic spectrum of both LOPD and IOPD and captures the biomarker profile and response to ERT in both populations. The QSP model was then applied to generate digital twins of each IOPD patient enrolled in the avalglucosidase alfa clinical development program, considering their individual disease burden, demographics (age, sex, body weight), and prior treatment history.

This digital twin cohort supplemented clinical observations by comparing the simulated tissue glycogen clearance and resulting biomarker response following alternative ERT regimens for each individual digital twin. Since all digital twins were simulated with all treatments, this addressed the confounding effects of baseline disease heterogeneity and treatment history that complicate interpretation of clinical observations. This analysis illustrates the power of the QSP-based digital twin approach to supplement clinical datasets in rare and highly heterogeneous indications, supporting the interpretation of efficacy results.

Case Study 10: Digital twin-based quantification of similarity of disease and treatment response between pediatric and adult patients. QSP models hold great promise to support the extrapolation of efficacy to different patient populations, especially in rare diseases.[55–57] The basis of the use of a QSP model for pediatric extrapolation is that if a QSP model intended to describe adult clinical data can describe with similar accuracy pediatric clinical data, then it can be inferred that the representation of disease and drug response is similar in both populations. This is achieved by calibrating the QSP model to the biomarker and clinical end-points profiles of individual adult patients (adult digital twins) to establish the expected degree of variability needed in each of these key pathophysiological processes and their associated parameters to accurately capture the observed adult data. The variation observed for the same processes and parameters in pediatric patients can then be

evaluated against this benchmark, by calibrating the model against the pediatric dataset (pediatric digital twins) and comparing the resulting adult vs. pediatric digital twins. This type of assessment can be used to mechanistically compare the exposure and response relationships in these populations to quantify the degree of similarity and support pediatric extrapolation. The following section describes a case study where a QSP-based assessment of similarity of disease and treatment response provided a valuable tool in pediatric drug development in a rare disease.

Acid sphingomyelinase deficiency (ASMD, historically known as Niemann-Pick disease, types A, B, and A/B; ORPHA:618899), is a rare, serious, life-threatening lysosomal storage disease due to insufficient activity of the lysosomal hydrolase acid sphingomyelinase (ASM). ASMD is caused by recessively inherited mutations in the sphingomyelin phosphodiesterase 1 (SMPD1) gene, encoding the enzyme ASM, which catabolizes sphingomyelin into ceramide. Deficiency of ASM results in the toxic accumulation of sphingomyelin in macrophages residing in various organs and in hepatocytes, resulting in tissue damage and organ dysfunction in patients with ASMD, such as lung function decline and splenomegaly.[58] The clinical development of olipudase alfa (commercialized as Xenpozyme) the first treatment for ASMD, included (i) a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial (DFI12712) in adult patients with ASMD; and (ii) a single arm open-label study (DFI13803) in pediatric patients. The two primary efficacy end points were % predicted diffusion capacity for carbon monoxide (% predicted DLco) and spleen volume in combination with the splenomegaly related score. The adequate and well-controlled pivotal study (DFI12712) in adults with ASMD showed a clinically meaningful and nominally statistically significant improvement in lung function and spleen size reduction for patients randomized to olipudase alfa compared to those treated with placebo at week 52. In pediatric patients with ASMD from a single arm open-label study, treatment with olipudase alfa resulted in similar improvements in lung function and spleen volume at week 52 as compared to baseline. The effectiveness of olipudase alfa in pediatric patients was based on this dataset and complemented with the framework of partial extrapolation. A QSP model was applied to assess the degree of mechanistic similarity of disease and response to treatment with olipudase alfa in pediatric and adult ASMD patients.[59] The QSP model described key visceral pathophysiology and the MoA of olipudase alfa with four sub-models that cover multiple biological scales of ASMD and olipudase alfa action. These include a pharmacokinetic (PK) sub-model, a molecular-level sub-model to describe two biomarkers (plasma ceramide and plasma lyso-sphingomyelin), a cellular-level sub-model, and an organ-level sub-model to describe two clinical end points (spleen volume and % predicted DLco) used for the clinical assessment of ASMD disease severity and response to olipudase alfa.

The analysis involved generating digital twins for each adult and pediatric ASMD patients enrolled in the olipudase alfa clinical program.[59] These digital twins were used to evaluate the similarity of baseline and treatment response of biomarkers and clinical end points between adult and pediatric patients by quantifying how comparable was the model description of the pediatric vs. adult datasets. This was achieved by comparing pediatric vs. adult digital twins against observed data, to evaluate whether digital twins capture their corresponding pediatric or adult patient's PK, PD, and clinical end points with comparable accuracy, regardless of age. The parameter value distributions and parameter sensitivities from adult digital twins and pediatric digital twins were also compared.

QSP-based digital twins captured each patient's observed biomarker and end-point profile, their demographic data, and the intrinsic variability in disease severity, all connected to a unified representation of ASMD. While sharing the same model structure, adult and pediatric digital twins showed comparable parameter value distributions, independent of age, for parameters that control key disease processes in ASMD phenotype. Consistent parameter sensitivities were also identified in both pediatric and adult digital twins. The QSP analysis results provided mechanistic insight into ASMD and suggested that there are no distinct patient sub-populations defined by age, but a continuum of disease presentations due to variability in disease severity. Applying the QSP model of ASMD in the olipudase alfa pediatric investigation plan informed drug development decision making, supported disease and treatment response similarity assessment, and extrapolation assumptions as well as facilitated the regulatory assessments and pediatric approval.

CONCLUSION

QSP-based analyses can provide insights into disease processes and drug action as exemplified by the case studies presented. The list of case studies presented here is by no means exhaustive, nonetheless it provides a glimpse to the potential impact that QSP analyses can have on drug development programs in rare indications. In early drug development, QSP models can facilitate the clinical translation of preclinical efficacy by providing biological mechanism-grounded bridging between preclinical experimental measurements and clinical metrics of pathophysiology to predict efficacy in the target patient population. QSP-based analysis can also support late phase clinical trials by generating digital twins to gain mechanistic insight into the disease presentation and treatment response observed. Overall, QSP models can function as repositories of the amalgamation of datasets related to the rare disease of interest. In some cases, they can complement the limited clinical trial data available and provide the means to evaluate the totality of knowledge on the disease and drug response.

Nevertheless, the successful application of QSP is not without hurdles. Beyond the technical challenges inherent to QSP approaches due to their complexity and uncertainties, these models necessitate a comprehensive understanding of the disease's etiology to deliver a meaningful analysis.[21,60] This involves linking the known pathophysiology and a description of the drug's MoA to observed biomarkers or clinical end points in a biologically meaningful manner. Monogenic diseases account for at least 80% of all rare diseases,[61] making them amenable indications to describe with a QSP framework given their more evident causality. Striking the right balance of how much mechanistic detail to include in a QSP model is key, with a fit-for-purpose and parsimonious model usually the goal. This requires

an evaluation of the features of disease pathophysiology necessary for the desired model application while maintaining a focused scope. Ambiguity or large gaps in knowledge that prevent a mechanistic description of the disease or observed response can limit the value of QSP-based approaches and may benefit from a more empirical modeling approach. This is particularly relevant for multifactorial diseases, where the interplay of multiple genes and environmental factors can influence disease phenotype and progression, which may be challenging to fully account for in a mechanistic model.

The growing number of QSP models applied throughout the drug development process[62] calls for the creation of assessment criteria and quantifiable metrics of QSP model quality. Given the complexity and time costs of model development, establishing rigorous quality metrics is pivotal for advancement of the QSP approach. These metrics would be analogous to those developed in established modeling approaches, and would increase confidence in QSP model performance.[63] Such standards could bolster stakeholder and regulatory acceptance, thereby fostering the routine integration of these mechanistic models in drug discovery and development.[64] While there are still many challenges to overcome, the potential benefits of the QSP approach are vast and could significantly accelerate drug development, delivering life-saving drugs for patients in rare diseases.

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SZ and CK are employees of Sanofi and may own stocks or stock options.

1. Orphan Drug Act <https://www.fda.gov/media/99546/download>.
2. REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141>.
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