

## CONFERENCE PROCEEDINGS

# Making Every Subject Count: A Case Study of Drug Development Path for Medication in a Pediatric Rare Disease

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**Approximately 50% of rare diseases are evident in children. Fatal disease prognosis and lack of treatments causes 30% of affected children to not live past their fifth birthday. This clear sense of urgency demands innovation and acceleration in drug development. A case study is discussed highlighting the need for data-rich phase I study design, extensive use of modeling and simulation, use of diverse data sources, and input from collaborators to respond to this urgent call.**

As suggested by Richter *et al.*,<sup>1</sup> there is no universal definition of rare disease but harmonization based on objective criteria, such as prevalence threshold is needed. Three basic tenets, however, are crucial to drug development in rare diseases: the sense of urgency, small numbers of patients, and the need for end-to-end planning early in the process. Urgency follows from unmet need in rare disease patients, who are often children based on the genetic origin, yet good clinical development principles are the core of drug development so continued innovation is even more crucial. As Bashaw *et al.*<sup>2</sup> point out, clinical pharmacology is at the cornerstone of drug development in rare diseases and clinical pharmacologists can address many of the

challenges that develop when working quickly yet maintaining high quality.

To optimize dose selection on this accelerated path, clear understanding of the information obtainability and gaps are needed. First, what is the therapy type? Biocorrection or target based? For diseases that need biocorrection through protein/enzyme replacement therapy, such as hemophilia or Gaucher disease, there might be a good understanding of required concentration levels, physiology pathways, and biomarkers. However, because the disease is rare, there may not be information about extensive pharmacokinetics (PKs) and safety information or robust descriptions of the variability of the endogenous proteins in healthy subjects. For target-based

therapies, extensive PK and safety data are more easily collected from healthy volunteer studies, but optimal target coverage, and how to bridge from healthy subjects to the patient population, is more difficult to define.

As with all clinical development, study designs need attention to be paid to knowledge of disease pathology and natural progression, patient availability, extent of observation required, and prior treatment knowledge for molecules in the same or related diseases. Early learnings might be gained from modified first-in-human (FIH) studies; for example, an assessment of dose response on muscle mass and fat mass for programs investigating Duchenne muscular dystrophy (DMD) has been gained by enrolling postmenopausal women in FIH studies (these women, like patients with DMD, have reduced muscle mass and increased fat mass).<sup>3,4</sup>

Due to the small numbers of available patients and desire of patients to avoid treatment with placebo or standard of care, natural history data play a pivotal role.<sup>5</sup> One of the pivotal studies with alglucosidase alpha for the treatment of infantile onset Pompe disease was an 18-patient open-label study in which the comparator placebo arm was derived from a subset of a natural history dataset (62 of 168 patients) with similar characteristics. The primary endpoint of survival free of invasive ventilation at 18 months was overwhelmingly (40-fold) in favor of the active arm (83% vs. 2%).<sup>6</sup>

Many rare diseases result in significant morbidity and mortality in children, a population rarely included in clinical studies unless there is a compelling need, so bridging from adults to pediatrics becomes a primary challenge that needs addressing very early in the clinical program. The problem is sadly compounded in many diseases by

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**Table 1** Mean of the 5th, 50th, and 95th quantiles for BWT, CL, and Vss in patients with DMD of age 6 and 10 years

Method	Age	Parameter	5th	50th	95th
Pooled mean and SD	6				
Four-species allometry		CL (mL/hr)	2.05	3.14	4.14
		CL (mL/hr/kg)	0.136	0.146	0.164
		Vss (mL)	904	1,498	2,076
		Vss (mL/kg)	68	70	72
Pooled mean and SD	10				
Four-species allometry		CL (mL/hr)	2.58	4.40	6.05
		CL (mL/hr/kg)	0.124	0.134	0.154
		Vss (mL)	1,190	2,236	3,261
		Vss (mL/kg)	67	68	71
Fixed exponent allometry	6	CL (mL/hr)	2.35	3.57	4.66
	10	CL (mL/hr)	2.89	4.91	6.68

BWT, body weight; CL, clearance; DMD, Duchenne muscular dystrophy; Vss, volume of distribution at steady state.

patients not surviving to adulthood or manifesting the disease quite differently. The case study to be presented demonstrates how clinical pharmacology data, in conjunction with modeling and simulation, can be used to bridge between populations.

PF-06252616, a monoclonal antibody against myostatin, is currently under development for treatment of DMD. Clinical development started with an FIH study (Clinicaltrials.gov identifier #NCT01616 277) with weight-based dosing in healthy adults followed by a phase II study in pediatric patients with DMD aged 6 to 10 years old (Clinicaltrials.gov NCT02310 763).<sup>7</sup> The FIH study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. The FIH study generated safety, PKs, and myostatin modulation over a wide dose range for both i.v. and s.c. single and repeat dosing. Importantly, the safety profile of PF-06252616 supported its subsequent development in children with the key emphasis being on dose selection. Three key steps in selecting doses for the pediatric population were undertaken: assessment of suitability of allometric scaling of PK properties for other similar monoclonal antibodies across adults and children, assessment of the causes of between-subject variability of PF-06252616 PKs in the available adult

population, and consideration of likely patient demographics to allow prediction of exposure in the patients of interest. The ultimate goal was to ensure that every patient contributed to meaningful data by reducing the likelihood of futile doses by leveraging all available (internal and external) information.

First, a meta-analysis was conducted comparing clearance (CL) and volume of distribution at steady state (Vss) for monoclonal antibodies between adult and pediatric patients. The meta-analysis showed that for monoclonal antibodies, body weight-adjusted dosing may be sufficient to bridge between adult healthy subjects and pediatric patients with DMD. Importantly, this meta-analysis provided confidence in the PK predictions to allow dosing at or near the expected efficacious concentrations.

The next step involved building a population PK/pharmacodynamic (PD) model using all available data from the FIH study and then using it to incorporate potential sources of variability and differences between populations. The FIH dataset used for population PK/PD model building was comprised of 1,671 observations of drug and myostatin concentrations from complete PK/PD time profiles of 36 subjects who received single doses of PF-06252616 across a wide dose range (1–40 mg/kg). The PK/PD model was validated with available PK/PD data from nine subjects in the multiple-dose cohort. A quasi-steady state model (where PF-06252616 binds to

myostatin to form a complex and all three entities are removed at different rates) was used to characterize the PK/PD data; model validation suggested that a better characterization of the nonlinear component may improve the fit at very low concentrations but this was not incorporated. Two factors were identified that could potentially account for variability between the populations and influence dosage selection; body weight and myostatin levels. A meta-analysis of 13 research articles with estimates of reported body weights for patients with DMD at or near the age bracket of interest (6–10 years old) was conducted and the pooled SD(s) were used to create weight distributions for the lower age (6 years) and upper age (10 years) brackets. Data on free/baseline levels of myostatin were not as widely available, but in association with key academic collaborators, it was determined that free myostatin levels were not increased in patients with DMD.<sup>8</sup> Myostatin coverage was then simulated using the quasi-steady state model, making the assumption that the levels were not different from the adult healthy subjects and higher levels of myostatin in patients with DMD would lead to suboptimal coverage.

The final step involved incorporating the body weight-scaled PK parameters into the population PK/PD model and assessing the appropriateness (from an exposure basis) of the proposed dosing regimens. Two methods of allometric scaling were

used to ensure full assessment of the potential impact of body weight on CL and  $V_{ss}$  in patients with DMD: a four-species allometric method (using noncompartmental PK parameters from mice, rat, monkey, and available human data) and a fixed exponent approach. The similarity of the exponents (0.79 and 0.94 for CL and  $V_{ss}$ ) from the four-species method to those expected for monoclonal antibodies indicate the appropriateness of this methodology. The weight distributions described earlier were then used with the derived allometric relationships to create distributions of CL and  $V_{ss}$  for patients with DMD 6 and 10 years old. The analyses suggested (Table 1) that if dosed per body weight, the corresponding CL values for the lightest (fifth percentile of age 6) and heaviest (95th percentile of age 10) patients with DMD would be 0.136 and 0.154 mL/hr/kg, which is a difference of only 13% and unlikely requiring different dosages. Similarly for  $V_{ss}$ , the corresponding values would be 68 and 71 mL/kg, which have a difference of <5%. Comparing the absolute CL values of the 5th, 50th, and 95th percentiles from the fixed exponent approach to the corresponding values in the four-species allometry approach, the maximum difference is <15% showing that using either method leads to similar CL estimates for patients with DMD. Hence, dosing in the subsequent phase II study in patients with DMD was proposed based on the strategy outlined here and has been accepted by seven regulatory authorities.

This case study provides an example of how all available internal data, literature

information, and input from external collaborations were leveraged to answer a range of questions and inform dose selection in patients with DMD. The combination of different analyses, including meta-analyses, population PK/PD modeling, and species-based and fixed allometric scaling methods, were used to confidently estimate exposure in 6 to 10-year-old patients with DMD. The robustness in prediction of PK parameters in pediatric patients (based on different methods) will hopefully mitigate against suboptimal exposures in patients with DMD. In summary, the fast track development in rare diseases creates a sense of urgency, requires the judicious use of the available patients, and demands innovation. Data-rich phase I study design, extensive use of modeling and simulation, use of diverse data sources, and input from collaborators may all be used to respond to this urgent call. Equally important is creating a culture, both within industry and regulators, where such approaches are supported or ultimately expected so that we may serve patients better.

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#### CONFLICT OF INTEREST

I. B., Z. M., P. C., L. H., and A. H. are employees of Pfizer Inc. and hold significant stocks and shares of Pfizer Inc.

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