Pharmacometric Analysis of Givinostat to Support Individualized Dosing Recommendations in Pediatric Patients with Duchenne Muscular Dystrophy

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Model informed analyses enabled rational simplification of the givinostat dosing regimen without compromising efficacy or safety.

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Background and Objectives

Givinostat is an oral histone deacetylase inhibitor evaluated in clinical studies for the treatment of Duchenne Muscular Dystrophy (DMD) in patients aged ≥6 years. Optimizing pediatric dosing while ensuring efficacy and safety required a model-informed approach due to ethical and logistical trial constraints common to rare diseases. A robust pharmacometric (PMx) strategy was implemented to overcome these challenges and support givinostat approval. The main objectives of the analysis were:

- To characterize the pharmacokinetic (PK) of givinostat and to quantify givinostat pharmacokinetic-pharmacodynamic (PK-PD) relationship with platelet levels using a model-based approach.
- To optimize dosing recommendations in DMD patients aged ≥6 years leveraging the developed PMx framework.

Methods

PMx analyses included data from six clinical studies (including one phase 2 and the pivotal phase 3 study EPIDYS in DMD patients). 3325 PK observations were available in 242 subjects, and 3241 PD observations (platelet counts) were available in 169 subjects. Demographics are presented in **Table 1**.

Table 1. Subject demographics for the PK and PK–PD analysis

Continuous covariates	Patients with DMD		Healthy adults (N=105)	Overall (N=242)
	6-11.9 years (N=119)	12-17.9 years (N=18)		
Age (yrs)				
Mean (SD)	8.99 (1.45)	13.2 (1.05)	33.7 (8.46)	20.0 (13.3)
Median [Min, Max]	8.90 [6.30, 11.9]	13.0 [12.0, 15.9]	32.0 [18.0, 55.0]	12.3 [6.30, 55.0]
Baseline weight (kg)				
Mean (SD)	29.0 (7.54)	39.7 (10.1)	76.9 (9.14)	50.6 (24.7)
Median [Min, Max]	27.2 [17.6, 59.6]	38.7 [28.8, 64.1]	77.1 [50.0, 98.0]	40.5 [17.6, 98.0]
Baseline platelet count (10^9/L)				
Mean (SD)	329 (70.0)	310 (75.6)	246 (48.9)	292 (73.7)
Median [Min, Max]	325 [164, 510]	295 [193, 492]	241 [150, 390]	281 [150, 510]

Abbreviations: DMD, Duchenne muscular dystrophy; Max, maximum; Min, minimum; SD, standard deviation.

A non-linear mixed effects approach in NONMEM was used for the population PK and PK-PD analyses. Model development was performed utilizing first-order conditional estimation method with interaction (FOCEI). The developed models were leveraged to simulate givinostat PK and PD in a virtual pediatric population > 2 years of age and > 10 kg (n=1000/weight group) based on age and weight distributions from the NHANES database [1]. Simulations accounted for inter-individual variability (IIV) and were performed in R using the package rxode2 (v 2.1.2). Simulated platelet counts were assessed biweekly; if predicted values were <150 × 10^9/L, dose reductions were applied. Simulated dosing regimens are presented in **Table 2**.

Table 2. Original (EPIDYS) and revised dosing regimens

EPIDYS dosing regimen									
Dose level		Patient weight (kg)							
		≥10 to <12.5	≥12.5 to <20	≥20 to <25	≥25 and <30	≥30 to <40	≥40 to <50	≥50 to <60	≥60 to <70	≥70
A	Dose (mg) BID	20	25	30	35	40	50	55	60	70
B	Dose (mg) BID	13.3	16.7	20.0	23.3	26.7	33.3	36.7	40.0	46.7
C	Dose (mg) BID	10.6	13.4	16.0	18.6	21.4	26.6	29.4	32.0	37.4
Revised dosing regimen										
Dose level		Patient weight (kg)								
		10 to <20		20 to <40		40 to <60		≥60		
Initial dose	Dose (mg) BID	25		35		50		60		
First dose modification	Dose (mg) BID	20		25		35		45		
Second dose modification	Dose (mg) BID	15		20		30		40		

Abbreviations: BID, twice daily.

PK-PD Models

A 2-compartment model with first order input with lag and first order elimination best described the PK of givinostat. IIV was incorporated on CL/F, V2/F and relative bioavailability (F), and residual variability (RUV) was addressed using a combined error model. The model included the effect of body weight on CL/F, with an allometric coefficient of 0.326 (95% CI 0.221-0.431). Parameters are presented in **Table 3**. A Friberg-like model [2] was used to describe the time course of platelet counts. An inhibitory linear drug model included on the proliferation rate (Kprol) parameter was used to describe the effect of givinostat on the platelet levels. Parameters are presented in **Table 4**. As supported by visual predictive check (VPC) diagnostics (**Figure 2** and **Figure 3**) both models described the data well and were therefore suitable for simulating givinostat PK and PK-PD in pediatric DMD patients.

PK-PD Simulations

The results of the simulations allowed simplifying the 9-weight band dosing regimen originally adopted in the EPIDYS study to a 4-weight band regimen (**Table 2**). In the revised regimen, geometric mean [CV%] simulated givinostat exposures were comparable in the 10–20 kg and 20–40 kg groups (area under the curve $AUC_{0\text{-}12}$: 380 [33.6] and 429 [33.4] hr•ng/mL) but slightly higher in the 40–60 kg and >60 kg groups ($AUC_{0\text{-}12}$ 504 [34.5] and 534 [33.6] hr•ng/mL) following the first administration (**Figure 1**). At steady-state, following final dose modifications, simulated exposures were comparable across all weight groups ($AUC_{0\text{-}12}$: 363 [32.0], 375 [32.0], 399 [32.8], and 415 [31.1] hr•ng/mL for 10–20 kg, 20–40 kg, 40–60 kg, and >60 kg groups, respectively).

Figure 1. Simulated single-dose $AUC_{0\text{-}12}$ following original (A,C; EPIDYS) and revised (B,D) givinostat dosing regimens

Boxes are the 25th and 75th percentiles, the line is the geometric mean, and whiskers are the 5th and 95th percentiles. The dark green line is the preclinical target (150 ng·h/mL). Green areas correspond to the exposure range of EPIDYS.

Dose reduction was required in 41.5% of virtual patients; most occurred within the first 3 months. The simulated percent of patients with grade 1 thrombocytopenia by weight band (EPIDYS vs revised) were as follows: 10 to <20 kg, 8.7% vs 11.1%; 20 to <40 kg, 28.5% vs 28.6%; 40 to <60 kg, 52.1% vs 48.5%; and ≥60 kg, 62.4% vs 59.7%. As shown in **Figure 4**, the platelet time course was simulated under 4 scenarios defined by combinations of baseline weight and platelet count. Higher weight and lower baseline platelet counts were associated with increased odds of requiring at least one dose reduction.

Conclusions

- The results from the pivotal Phase 3 study EPIDYS showed that the devised dosing instructions allowed to safely manage platelet decrease, with >95% of patients completing the study without clinical manifestations [3]
- The developed PMx framework allowed to successfully revise the regimen and to ensure consistent exposures across weight groups while substantially simplifying dosing and lowering the risk of thrombocytopenia-related reductions
- Individualized treatment is achieved by initiating givinostat at doses optimized for efficacy while allowing dose reductions
- Clinicians should consider both weight and baseline platelet count when estimating the likelihood of requiring dose adjustments

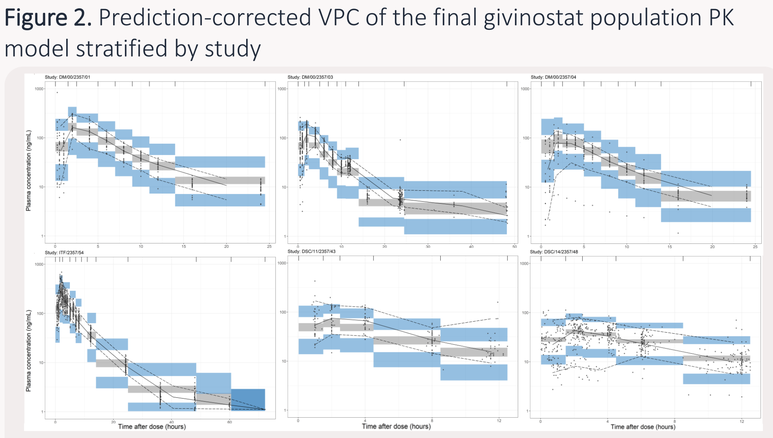
Additional Figures & Tables

Table 3. Parameters of the final givinostat population PK model

Parameter	Description	Estimate (Shrinkage %)	RSE (%)	Estimate (Natural Scale)
CL/F (L/h)	Estimated on log scale	4.76	1.0	117
V_2/F (L)	Estimated on log scale	5.33	1.4	206
Q/F (L/h)	Estimated on log scale	3.80	1.4	44.7
V_3/F (L)	Estimated on log scale	6.33	0.7	561
F (unitless)	Natural scale	1 (FIX)	NA	1 (FIX)
k_a (1/h)	Estimated on log scale	-1.19	2.4	0.304
Lag time (h)	Estimated on log scale	-1.49	1.8	0.225
Allometric coefficient on CL	$*(WT/40.5)^{\theta}$	0.326	16.4	0.326
Meal on F	$*(1+\theta)$	0.276	29.2	0.276
IIV on CL/F	Variance	0.037 (30.4)	29.7	
IIV on V_1/F	Variance	0.466 (17.6)	21.4	
IIV on F	Variance	0.0687 (19.8)	15.7	
RUV	Additive variance	0.0001 FIX		
RUV	Proportional variance	0.104 (5.5)	8.0	

Abbreviations: F, relative bioavailability; FIX, fixed in the model; NA, not available; RSE, relative standard error; WT, body weight; θ, fixed effect parameter.

Figure 2. Prediction-corrected VPC of the final givinostat population PK model stratified by study



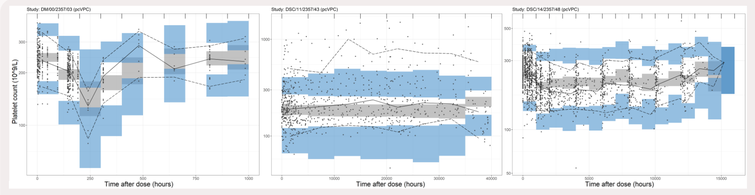
Symbols represent observations; solid thick line represents the median of the observations; dashed thick lines represent the 5th and 95th percentiles of the observations; colored bands represent 50th (grey), 5th and 95th (blue) percentiles of the model predictions with 95% CI. The study number is at the top left of each plot

Table 4. Parameters of the final population PK–PD model for platelet counts

Parameter	Description	Estimate (Shrinkage %)	RSE (%)	Estimate (Natural Scale)
Baseline platelets (10^9/L)	Estimated on log scale	5.76	0.3	316
MTT	Estimated on log scale	4.36	1.0	78.1
Slope mL/ng	Estimated on log scale	-7.0	1.09	0.00091
Proportional RUV	Variance	-1.89	2.1	0.150
Gamma	Estimated on logit	-1.86	4.9	0.0640
Weight on baseline	Log-linear	-0.251	12.8	-0.251
IIV on Baseline	Variance	0.0314 (7.7)	13.5	
IIV on MTT	Variance	0.0297 (50.1)	31.3	
IIV on Slope	Variance	0.183 (13.8)	22.9	
Additive error	Variance	0.00001 FIX	NA	

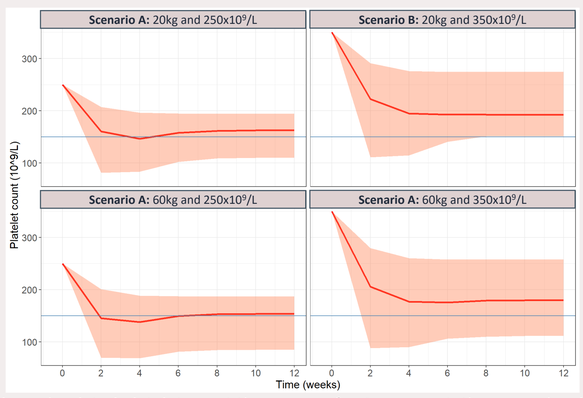
Abbreviations: FIX, fixed in the model; MTT, mean transit time; NA, not available; RSE, relative standard error.

Figure 3. Prediction-corrected VPC of the population PK–PD model for platelet counts following givinostat treatment stratified by study



In Study 03, givinostat treatment was given up to day 10 (240 hours after the first dose). Symbols represent observations; solid thick lines represent the median of the observations; dashed thick lines represent the 5th and 95th percentiles of the observations; dashed line represents the median of the model predictions; dotted lines represent the 5th and 95th percentiles of the model predictions, and colored bands represent 50th (gray), 5th, and 95th (blue) percentiles of the model predictions with 95% CI.

Figure 4. Simulated platelet count time courses across 4 patient scenarios



Panels show simulated platelet count time course for 4 representative scenarios defined by baseline body weight and baseline platelet count. The red solid line represents median platelet counts across 1000 replicates; the shaded area represents the 90% prediction interval.

[1] https://wwwn.cdc.gov/nchs/nhanes/
[2] Friberg LE et al. Model of chemotheraphy-induced myelosuppresion with parameters consistency across drugs. J. Clin. Oncol 20:4713:4721, 2002.
[3] Mercuri E et al. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2024 Apr;23(4):393-403.

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