

Dose Selection Process for Younger Children Participating in a Phase 3 Study to Evaluate the Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-occlusive Crisis in Hospitalized Patients With Sickle Cell Disease

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INTRODUCTION

- Rivipansel is a pan-selectin inhibitor in development for the treatment of vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD)
- Rivipansel inhibited inflammation in several animal models of the disease, including the mouse model of VOC in SCD
- A single phase 3 study was planned to evaluate the efficacy and safety of rivipansel (formerly GMI-1070) in the treatment of VOCs in hospitalized patients with SCD
 - Selection of the dose to be used in this study was based on the efficacy, safety, and pharmacokinetic (PK) results from the rivipansel phase 2 study
 - Modeling and simulation (M&S) was used to determine the dosing for adults and children aged >6 years with SCD
 - The trial contained two cohorts, cohort 1: adults and children aged ≥12 years, and cohort 2: children aged 6–11 years
- To assess whether the actual drug exposure in cohort 2 is comparable to the model based predicted drug exposure, we conducted a blinded review of PK data obtained from several patients enrolled in cohort 2; the methodology around this evaluation is presented.

METHODS

- PK data for 109 patients receiving doses of 2–40 mg/kg in 4 previous studies (three phase 1, one phase 2) were integrated to build a 3-compartment model, which was used to perform simulations to aid dose selection
- As rivipansel is almost entirely renally excreted, the simulations of clearance (CL) were based on renal function involving hyperfiltration, representing an altered renal filtration, common in SCD patients¹
- The covariance matrix of demographics (age, weight, height, and creatinine across sexes) from the phase 2 study² was used to simulate demographics in older children (aged 12–17 years) and adults in the target SCD patient population
- This model allowed for scaling of the PK exposure from the model developed in adults and older children^{3,4} to younger children (aged 6–11 years)
- Cohort 1: based on PK data from phase 2, children aged ≥ 12 years and adults received a loading dose of 1680 mg and subsequent maintenance doses of 840 mg q12h
- Cohort 2: a range of dosing regimens were explored through simulations
 - 20-mg/kg loading dose followed by 10-mg/kg maintenance dose every 12 hours (q12h; 20/10 mg/kg)
 - 30-mg/kg loading dose followed by 15-mg/kg maintenance dose q12h (30/15 mg/kg)
 - 40-mg/kg loading dose followed by 20-mg/kg maintenance dose q12h (40/20 mg/kg), as the highest employed dosing regimen
- The resulting simulated exposure distributions from 3 dosing regimens were compared with the efficacious average concentrations at steady state ($C_{avg,ss}$) observed in the phase 2 study² and used to select the dose for cohort 2 in phase 3
- Early in the phase 3 trial, during a blinded review, concentration-time profiles for the first 6 actively treated children from cohort 2 were generated, and Empirical Bayes estimates (EBEs) of the individual PK parameters (eg CL, V_{ss}) and their corresponding $C_{avg,ss}$ were derived
- To confirm the predicted exposure in those children, age- and weight-dependent cumulative distribution functions (CDF) of parameters in the population PK model (eg, CL, V_{ss}) and the corresponding $C_{avg,ss}$ were derived through simulations and compared with the EBEs
- The percentiles in which the EBEs fell within the simulated CDFs from the model were used to guide the decision for a potential dose adjustment and this process is outlined in the flow chart in **Figure 1**

RESULTS

- The PK data from the phase 2 study supported fixed flat dosing for patients aged ≥ 12 years (cohort 1)
- PK M&S predicted that a loading dose of 1680 mg followed by a maintenance dose of 840 mg q12h would result in exposures similar to those observed with the lower dose used in the phase 2 study, such that a minimum plasma concentration of $>10 \mu\text{g/mL}$ would be maintained throughout the dosing interval
- For patients in cohort 2, weight-based dosing was considered, as it is the most conservative approach, given that children in this age range have not been studied before
- For each dosing regimen tested, the simulated demographic target distribution in pediatric SCD patients was used to derive concentration-time profiles
 - Simulations from the model in the adult and pediatric population are presented in **Figure 2**

Figure 2. Simulated Concentration-Time Profiles After Different Dosing Regimens Across the Age Range to Be Studied

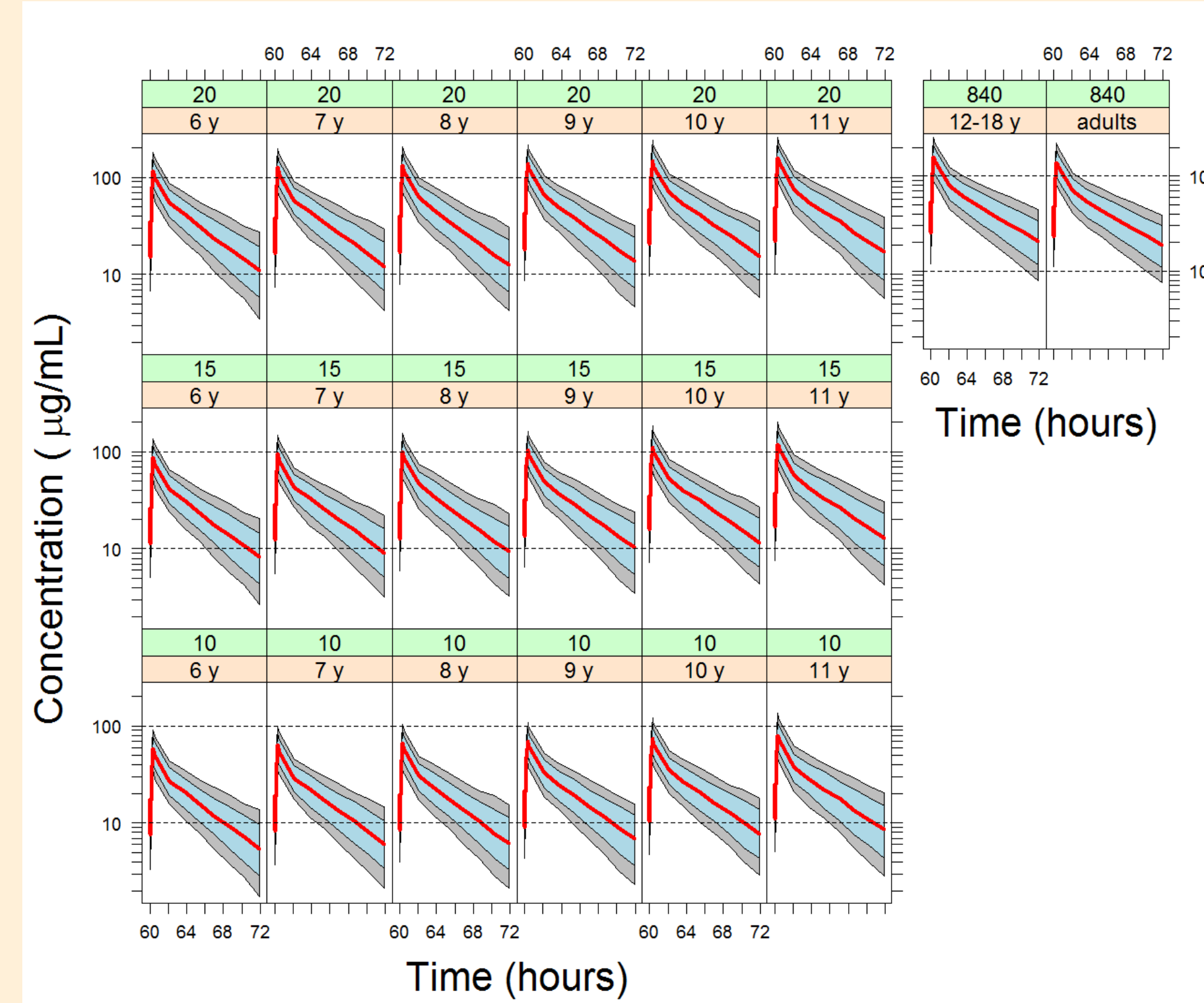


Figure 3. Cavg,ss Distributions at Different Dosing Regimens Across the Age Range to Be Studied

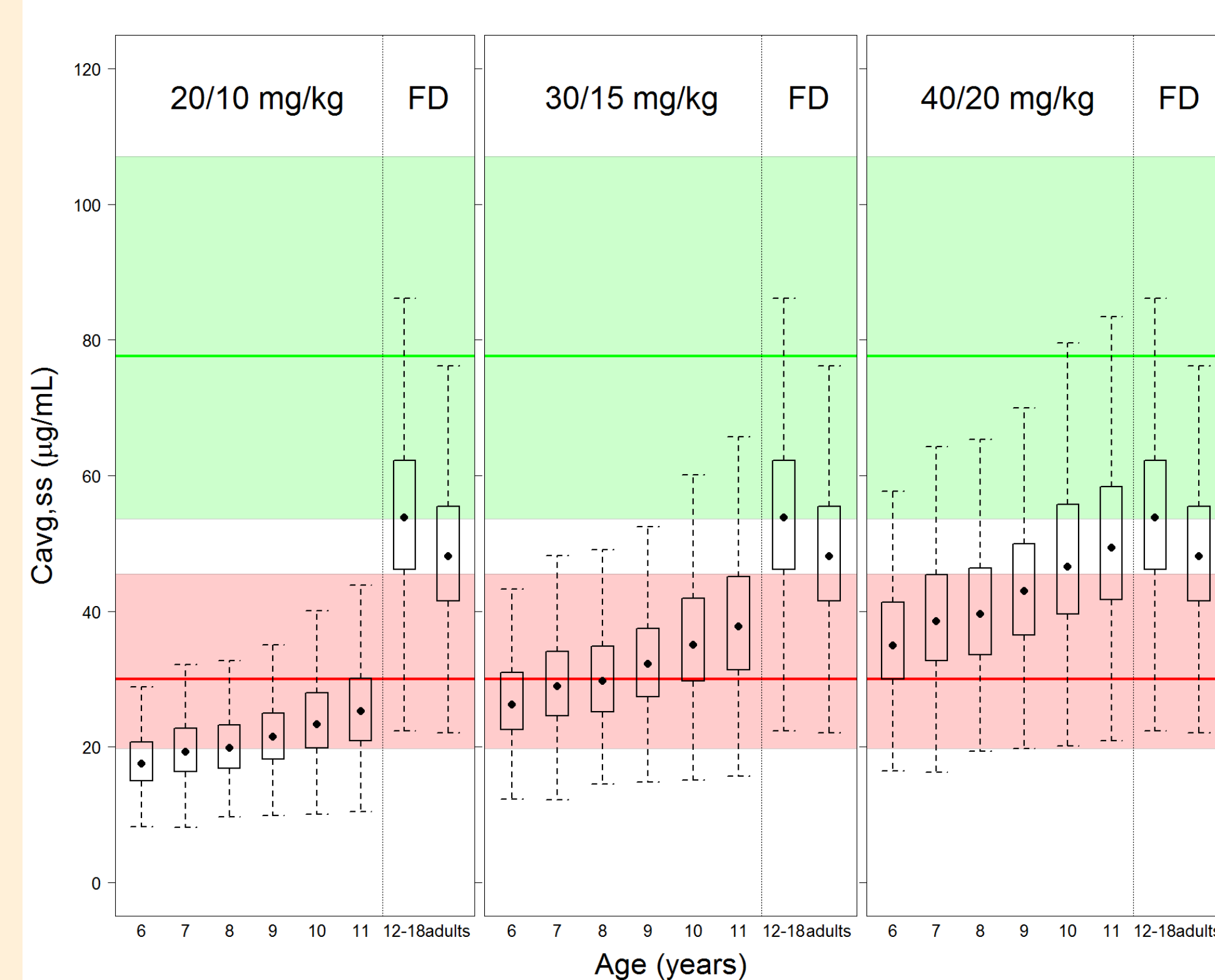
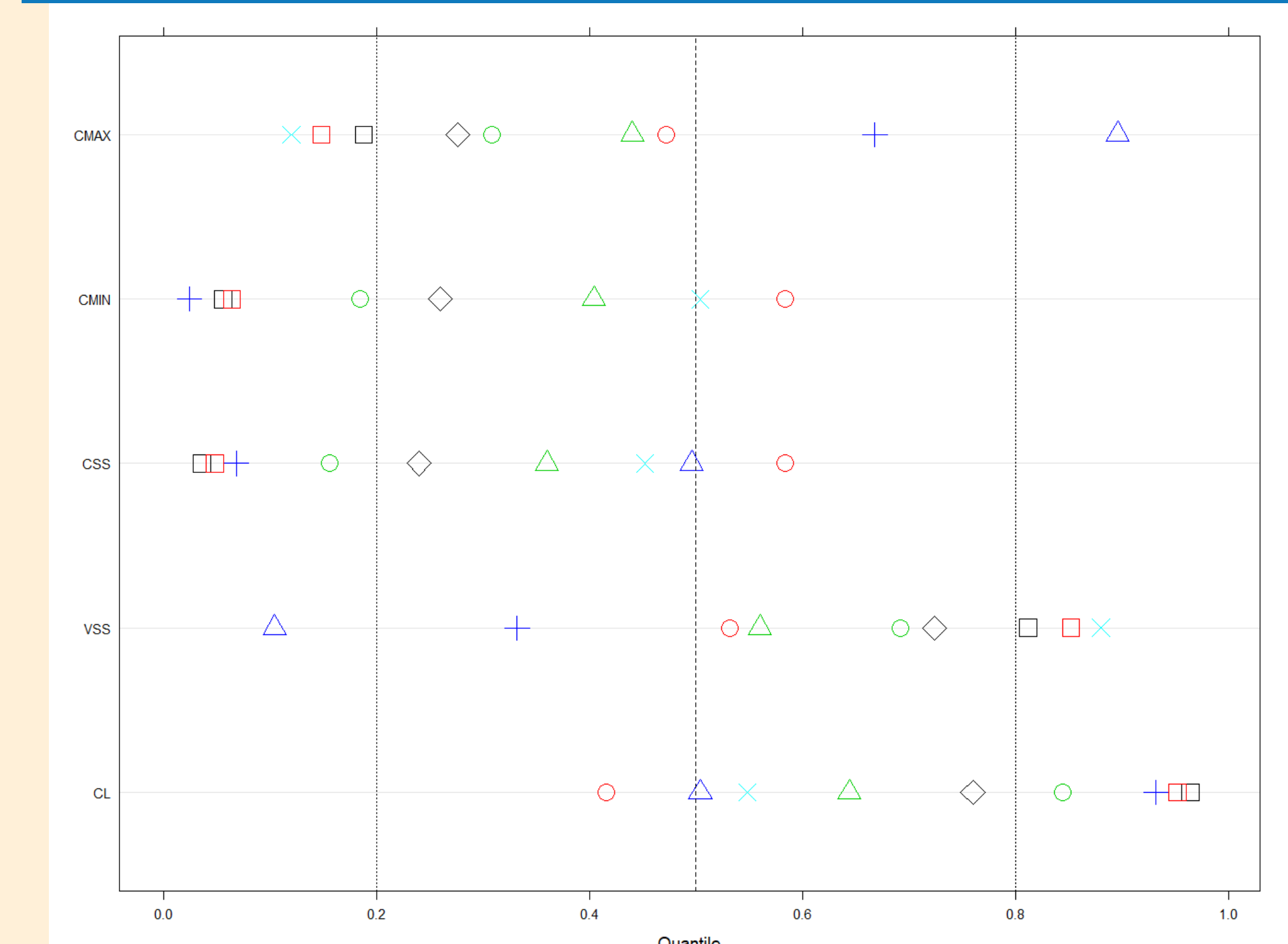


Table 1. Simulation of decision criteria based on varying cohort samples sizes and assumptions on biases

			Decision criterion on Css,avg				
	Assumption		Test on EBEs		Test on simulated percentiles		
Number of Patients in cohort	bias in true CL (H0=1)	bias in true ω^2 (H0=1)	median >20<80 ug/mL	CV in sample <30%	normality test (shapiro)	median within 40% PI	> 50% of samples w/ i 68% P
6			1	0.662	0.946	0.762	0.724
12	1	1	1	0.636	0.95	0.865	0.834
18			1	0.625	0.927	0.944	0.909
24			1	0.66	0.943	0.965	0.948
6			0.984	0.607	0.934	0.087	0.193
12	0.8	1	0.998	0.644	0.881	0.019	0.163
18			1	0.669	0.796	0.014	0.171
24			1	0.652	0.749	0.003	0.144
6			0.439	0.634	0.724	0	0
12	0.6	1	0.417	0.623	0.345	0	0
18			0.401	0.663	0.089	0	0
24			0.377	0.66	0.009	0	0
6			0.999	0.502	0.95	0.629	0.51
12	1	1.5	1	0.44	0.917	0.8	0.633
18			1	0.435	0.895	0.863	0.699
24			1	0.419	0.867	0.909	0.763
6			0.974	0.515	0.921	0.123	0.183
12	0.8	1.5	0.995	0.456	0.849	0.058	0.154
18			0.998	0.399	0.779	0.029	0.139
24			1	0.41	0.687	0.015	0.109
6			0.455	0.536	0.733	0	0
12	0.6	1.5	0.463	0.425	0.443	0	0
18			0.435	0.406	0.153	0	0
24			0.404	0.414	0.028	0	0

- A summary of the $C_{avg,ss}$ distribution across different ages is shown in **Figure 3**; the simulations showed that for children aged 6–11 years, a 40-mg/kg loading dose (maximum 1680 mg) followed by 20 mg/kg every 12 hours (maximum 840 mg) would most likely result in concentrations similar to those observed with the 20/10-mg/kg dosing used in adults in the phase 2 study
- An exemplified blinded assessment of the exposure distribution during the phase 3 trial in an initial cohort of 6 children, including the percentiles in which their EBEs fell within the simulated CDFs from the model, is shown in **Figure 4**

Figure 4. Simulated Percentiles for Each Patient's Empirical Bayes Estimates in Cohort 2 (Children Aged 6–11 Years)



The graph illustrates a simulated population of 6 patients. Each line corresponds to a parameter (CL, V_{ss}) or derived measure ($C_{avg,ss}$, C_{min} , C_{max}) from the population PK model. For each estimated individual parameter, the EBE (point), derived using the PK samples in a given patient and the population PK model, is added at the corresponding percentile of the CDF as simulated for a given patient from their demographics (sex, age, weight, height, and dose).

C_{avg,ss}, average steady-state plasma concentration; C_{max}, maximum serum concentration; C_{min}, minimum plasma concentration; CDF, cumulative distribution function; CL, clearance; EBE, empirical Bayes estimate; V_{ss}, steady-state volume of distribution.

- An assessment of the outcome of various decision criteria applied to simulations of PK cohorts varying in size is shown in **Table 1**.
- All scenarios test for consistency with the prior knowledge, and a set of alternative assumptions on clearance and its variability.
- Consecutive sample sizes from 6 – 24 PK sample were simulated 500 times and the decision rules applied to the Empirical Bayesian estimates representing individual paediatric cohorts.
- Alternative decision rules based on percentile distribution based on simulations from the published model were performed as well.
- While an improvement in the correct decision to either maintain or change the dose is improving with increasing samples sizes, also the percentile approach appears to be more sensitive to highlight deviations which may earlier lead to dose adjustment decisions.

CONCLUSIONS

- A population PK model for rivipansel has been developed, applicable to the whole target SCD population of adults and children aged ≥ 12 years
- Its applicability in children aged 6–11 years is under investigation as part of an ongoing phase 3 study, and interim assessments of the PK exposure have been done in small cohorts of 6 patients
- The corresponding decision framework has been implemented and exercised successfully, with the results of potential dose adaptations to be published once the phase 3 study has been concluded

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AUTHOR DISCLOSURES

All authors are employees of Pfizer Inc and may own stock/options in the company.

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Figure 1. Decision Flow Chart to Assess PK Exposure in Children Aged 6–11 Years as Part of the Ongoing Phase 3 Trial

