

Population Pharmacokinetics of Belimumab Administered Intravenously in Children with Systemic Lupus Erythematosus

Poster III-31 | Abstract 8985



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Background

- Belimumab (BENLYSTA) is a human IgG1 λ monoclonal antibody that neutralizes B-cell activating factor (BAFF; also known as B-lymphocyte stimulator protein, BLyS)
- Patients with Systemic Lupus Erythematosus (SLE) have elevated levels of circulating BAFF, which promotes abnormal B cell activation and differentiation
- Childhood-onset SLE (cSLE) is rare but has higher disease activity, increased rates of renal, neurologic, and hematologic involvement, and faster damage accrual over time compared with adult-onset SLE
- Pharmacokinetic (PK) results from a Phase 2, multicenter, randomized, double-blind, placebo-controlled study in pediatric patients with active cSLE (PLUTO Part A; NCT01649765; GSK study 114055) are presented here.
- Belimumab administered intravenously (IV) was approved for the treatment of active SLE in adults (2011) and in children aged 5 year or older (FDA, April 2019).

Objectives

- To characterize the population PK (popPK) of belimumab following IV administration in pediatric patients with cSLE and evaluate the potential effect of selected covariates on PK parameters.
- To compare belimumab exposure in pediatric patients with cSLE to exposure in adult SLE Phase 3 patients with IV administration.

Methods

- Patients with cSLE were randomized to the weight-normalized belimumab dose of 10 mg/kg approved for adults or placebo, administered on Days 0, 14 and 28, and every 28 days thereafter for 52 weeks.
- PK data were provided by the 53 patients on active treatment, of which 20 patients were included in PK lead-in cohorts with more intense PK sampling (median 16.5 samples).
- Ten of the 53 subjects were in the younger age group (Cohort 2: 5-11 years of age).
- PK data were analyzed with a non-linear mixed effects modeling approach using NONMEM.
- Model development was guided by the previously developed popPK model for IV belimumab in adults [1].
- Results using a MAXEVAL=0 approach on the adult model were compared with a revised popPK model with covariate effects updated for pediatrics, re-estimating all model parameters, then reducing the model with a variation of the full model approach [2].
- Individual post-hoc parameters were used to derive steady-state PK profiles and exposure parameters (e.g. Cavg, average serum concentration over the 28-day dosing interval), which were compared to the corresponding adult Phase 3 results.

Results

- The final popPK model described the pediatric belimumab PK as a linear 2-compartment model with clearance from the central compartment (CL).
- The population estimates for central clearance, steady-state volume of distribution and terminal half-life were 158 mL/day, 3.5 L, and 16.3 days, respectively, in the overall pediatric population (Table 1).
- Fat-free mass (FFM) [3] best described the effects of body size on the PK.
- Age did not have a statistically significant effect on clearance after accounting for body size effects.
- Additional covariate effects retained in the final model were baseline IgG, proteinuria, and estimated glomerular filtration rate on CL, and baseline white blood cell count on central volume V1.
- The visual predictive check confirmed that the central tendency and between-subject variability predicted by the model matched the observed exposures across the duration of Part A (Fig. 1B). Figure 1B show the slightly inferior predictive performance of the MAXEVAL=0 model.

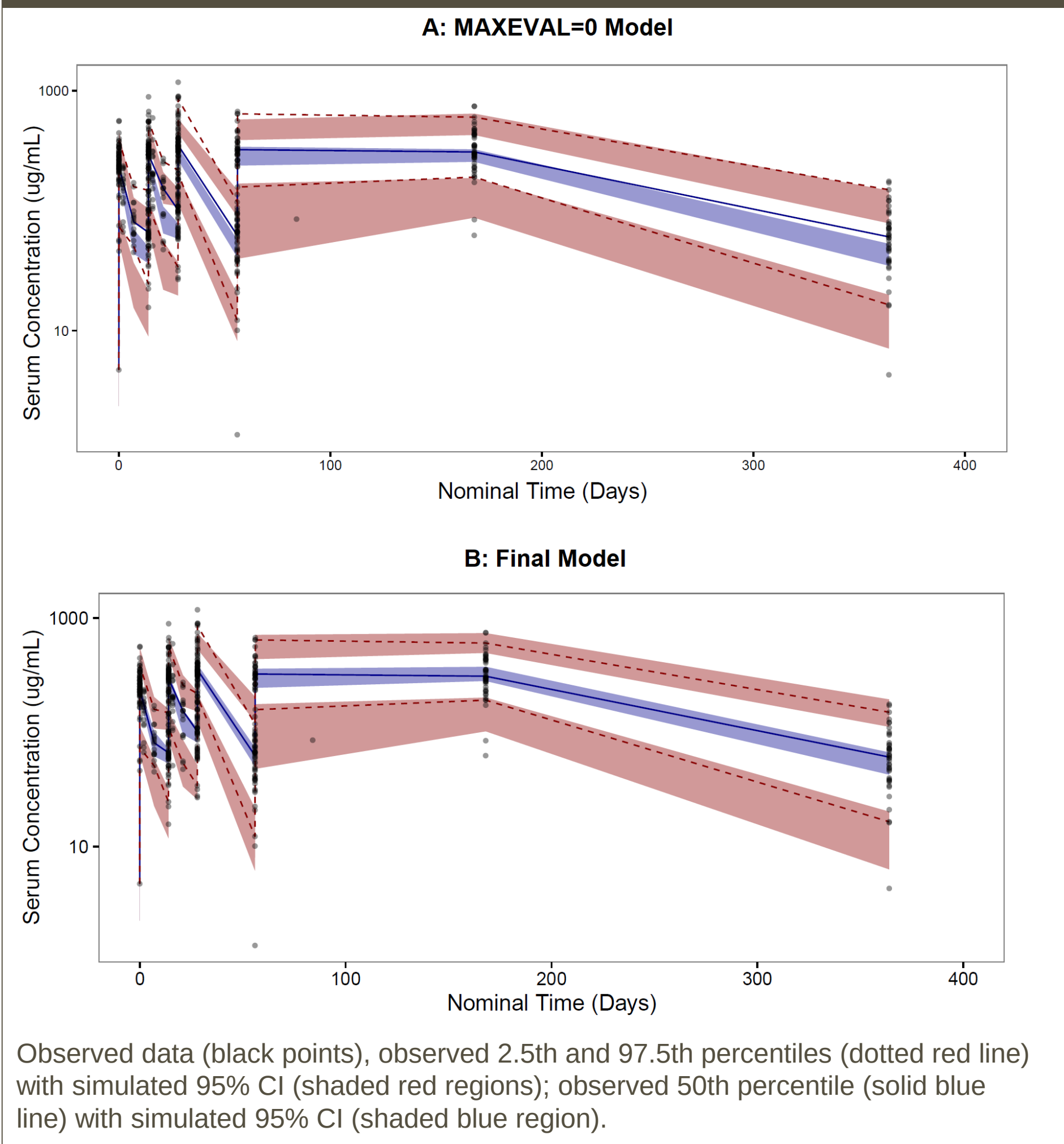
Table 1: Population Parameter Estimates

Parameters	Model Point estimate (%RSE, 95% CI)	Bootstrap ^a Median (95% CI)
Fixed effects		
CL (mL/day)	158 (3.62%, 147-169)	157 (142-169)
x (BFFM/34.4) ^o	0.691 (18.6%, 0.439-0.942)	0.691 (0.418-0.963)
x (BEGFR/105.21) ^o	0.561 (34.4%, 0.183-0.939)	0.510 (0.079-0.966)
x (BIGG/14.5) ^o	0.396 (24.8%, 0.204-0.588)	0.415 (0.237-0.639)
x (BPROT/0.132) ^o	0.184 (26.4%, 0.0888-0.279)	0.176 (0.082-0.289)
V1 (mL)	1927 (3.97%, 1777-2077)	1932 (1782-2090)
x (BFFM/34.4) ^o	0.944 (13.5%, 0.694-1.19)	0.941 (0.695-1.220)
x (BWBC/5.9) ^o	0.245 (39.9%, 0.0536-0.437)	0.242 (0.020-0.426)
Q (mL/day)	701 (18.6%, 445-957)	700 (150-931)
x (BFFM/34.4) ^o	See FFM on CL	
V2 (mL)	1622 (15.2%, 1138-2105)	1635 (1128-2157)
x (BFFM/34.4) ^o	See FFM on V1	
Inter-individual variability		
ω^2_{CL}	0.0477 (28.8%, 0.0207-0.0746)	0.0407 (0.0175-0.0674)
ω^2_{V1}	0.0620 (24.7%, 0.0320-0.0920)	0.0572 (0.0306-0.0888)
$\omega^2_{CL/V1}$	0.0366 (34.1%, 0.0122-0.0611)	0.0347 (0.0117-0.0590)
ω^2_{V2}	0.434 (29.1%, 0.187-0.681)	0.418 (0.203-1.413)
Residual variability		
$\sigma^2_{proportional}$	0.0884 (18.3%, 0.0568-0.120)	0.0871 (0.0603-0.120)
$\sigma^2_{additive}$	0.0139 (Fixed)	0.0139 (Fixed)

Abbreviations: %RSE=relative standard error as percentage of estimate; 95% CI=95% confidence interval of estimate; CL=clearance; V1=volume of distribution of central compartment; Q=inter-compartmental clearance; V2=volume of distribution of peripheral compartment; BFFM=baseline fat-free mass; BEGFR=baseline calculated estimated glomerular filtration rate; BIGG=baseline IgG levels; BPROT= baseline proteinuria levels; BWBC=baseline white blood cell count

^a Bootstrap parameters based on 1694 successful minimizations (out of 2000 attempts)

Figure 1: Visual Predictive Checks



- Variations of the body size effect were compared in the final mode (Table 2). There were no qualitative differences between the model fits. However, FFM estimated exponents were closest to values expected from allometry (0.75 for CL and Q, 1 for V1 and V2). In comparison, BWT alone yielded lower, while BWT & BMI yielded higher exponent values for the BWT covariate.

Table 2: Comparison of Body Size Effects

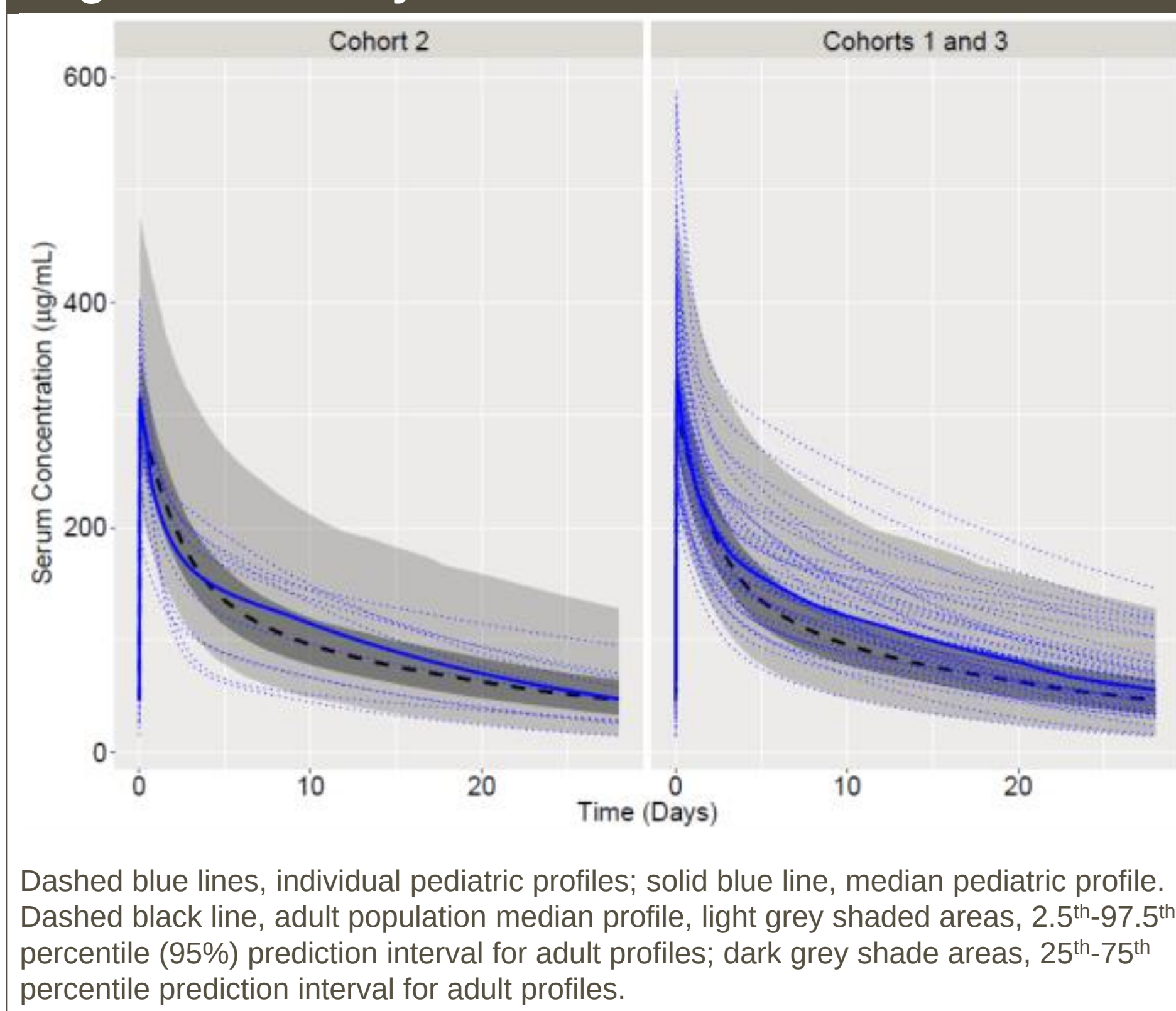
Body size covariate	Exponent (CL, Q)	Exponent (V1, V2)	Model OVF
Fat-free mass	0.691	0.944	5148.9
Body weight (BWT)	0.591	0.802	5150.1
Body weight & BMI	0.950 -0.727	1.14 -0.669	5145.9

- Belimumab Cmax, Cmin, and Cavg exposures for the overall pediatric study and both pediatric age groups were similar to adult exposure at the 10 mg/kg dose level in Phase 3 trials; younger subjects had slightly lower exposures than the older subjects (Table 3 and Figure 2).

Table 3: Steady-State PK Parameters

Param.	Cohort 2 (N=10): 5-11 Years	Cohorts 1 and 3 (N=43): 12-17 Years	Total Pediatric (N=53): 5-17 Years	Adult (N=563) See [1]
Cmax,ss (ug/mL)	305 (267-350)	317 (288-350)	315 (290-342)	311 (306-316)
Cmin,ss (ug/mL)	42 (30 - 60)	52 (43 - 63)	50 (42 - 59)	46 (44 - 48)
Cavg,ss (ug/mL)	92 (71 - 118)	112 (99 - 126)	108 (96 - 120)	100 (98 - 103)

Figure 2: Steady-State PK Profiles



Dashed blue lines, individual pediatric profiles; solid blue line, median pediatric profile. Dashed black line, adult population median profile, light grey shaded areas, 2.5th-97.5th percentile (95%) prediction interval for adult profiles; dark grey shaded areas, 25th-75th percentile prediction interval for adult profiles.

Conclusions

- The PK of IV administered belimumab is described by a linear two-compartment PK model for both adults and pediatrics.
- Individual pediatric PK parameters predicted by the adult popPK model using the MAXEVAL=0 approach were appropriate, but the final pediatric popPK model had superior simulation performance.
- Enriched sampling in PK lead-in cohorts (N=20) together with sparse sampling in other subjects (N=33) enabled the estimation of the popPK parameters with sufficient precision based on pediatric data only.
- For the approved weight-proportional dose of 10 mg/kg, the pediatric exposures (Cavg = 108 ug/mL) are similar to adults (Cavg = 100 ug/mL).
- The estimated allometric exponents on clearance and volume were consistent with values expected from allometric theory (0.75 and 1, respectively) when FFM was used to define body size, but somewhat lower when the total body weight was used. This important result suggests that for antibodies FFM may align more naturally with allometric theory to describe the influence of body size on clearance and distribution.
- These PK results support the approved adult IV dose of 10 mg/kg as an appropriate dose for pediatric patients with cSLE and that, other than weight-proportional dosing, no dose adjustments are required in the studied pediatric population.

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