Belimumab Pharmacokinetic Simulations to Select an Appropriate Subcutaneous Dosing Regimen to Treat Paediatric Patients with Active Lupus Nephritis

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Introduction

The cytokine B-cell lymphocyte stimulating protein (BLyS) plays an important role in the production and differentiation of B cells. Circulating levels of BLyS have been shown to be elevated in systemic lupus erythematosus (SLE), which is a chronic auto-immune disease with a complex pathophysiology[1]. Active lupus nephritis (LN) is a severe manifestation of the disease which affects the kidneys[2].

Belimumab (Benlysta) is a human immunoglobulin G (IgG) monoclonal antibody that binds to and inhibits BLyS and has been approved as an intravenous (IV) and subcutaneous (SC) formulation in adults with SLE[3,4] and active LN; approval of the SC dose in adults with active LN was based on PK bridging simulations.

In the paediatric (ped) population, IV belimumab was approved for SLE based on a pharmacokinetic (PK) and efficacy study[5], and for LN based on bridging PK simulations, both with the same dosing regimen as in adults.

Belimumab SC has recently been studied in paediatric patients with SLE. The current work presents PK bridging simulations to identify an appropriate belimumab SC treatment regimen for paediatric LN patients.

Objectives

- To construct a fit-for-purpose population PK model for paediatric LN patients receiving belimumab SC, based on previous population PK model analyses (Table 1) in both adult patients with SLE and LN and in paediatric SLE patients.
- To perform simulations to derive an appropriate SC dosing regimen and assess SC loading doses in paediatric LN patients to match the adult LN exposures for which safety and efficacy has been established.
- To explore body weight-belimumab exposure relationships to justify the SC dosing regimens.

Model name	Description	Population	Study name	Based on
Model A1	Analysis model	Adult SLE (SC)	BEL112341 (BLISS-SC)	Clinical study data
Model A2	Analysis model	Adult LN (IV)	BEL114054 (BLISS-LN)	Clinical study data
Model A3	Analysis model	Paediatric SLE (IV)	BEL114055 (PLUTO-IV)	Clinical study data
Model A4	Analysis model	Paediatric SLE (IV+SC)	BEL114055 (PLUTO-IV) 200908 (PLUTO-SC)	Clinical study data
Model S1	Simulation model	Adult LN (SC)	-	Model A1 and Model A2
Model S2	Simulation model	Paediatric LN (IV)	217143	Model A2 and Model A3

Table 1. Key Analysis and Simulation Population PK Models Developed In Earlier Studies.

Data

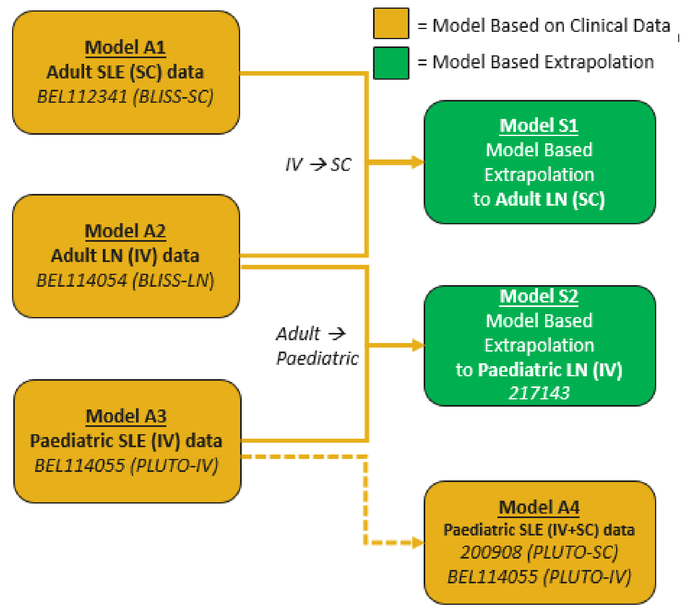

Figure 1. Key Analysis and Simulation Models Developed in Earlier Studies. Yellow boxes: analysis models based on clinical data with the model name, the fitted population data and the study name. Green boxes: simulation models, i.e. model based extrapolations, with the model name, the population that was extrapolated to and, if applicable, the study name

Methods

A fit-for-purpose model was constructed to simulate belimumab concentrations following SC dosing in paediatric LN patients 5-17 years and ≥15 kg.

The model was an extrapolation from an earlier model developed on adult LN IV data, replacing baseline fat-free mass (FFM) with baseline weight (BWT) scaling and including SC absorption parameters estimated from paediatric SLE IV+SC data. A clinical study in paediatric patients with active LN has not been carried out and so the PK model selected for this population was part-validated by comparing against the population PK model previously developed for paediatric SLE patients.

PK simulations were performed to select an appropriate dosing regimen, including a 4-week loading period, which ensured that exposures were consistent across the paediatric weight range whilst early exposures were aimed to be within the adult LN IV target range (41-161 µg/mL).

Model & simulation

Modelling rationale

- Available models have been developed for adult SLE, adult LN, and paediatric SLE, for both LN and SC administration
- A fit-for-purpose model for paediatric LN (SC) was constructed using these models.

General model structure of available models:

- Linear 2-compartment model with absorption
- Between-subject variability on clearance (CL, Q) and volume (V1 and V2) parameters, and proportional residual variability
- Covariates:
  - Body size (FFM or BWT) on CL, V1, Q, and V2
  - Time-dependent LN covariates (specific to model A2):
    - Albumin (ALB) on CL with proteinuria (PROT) interaction: $(ALB/42)^{\theta 1/(1+\theta 2*PROT)}$
    - PROT on CL: $1 + \theta*PROT$

Model Extrapolation Strategy

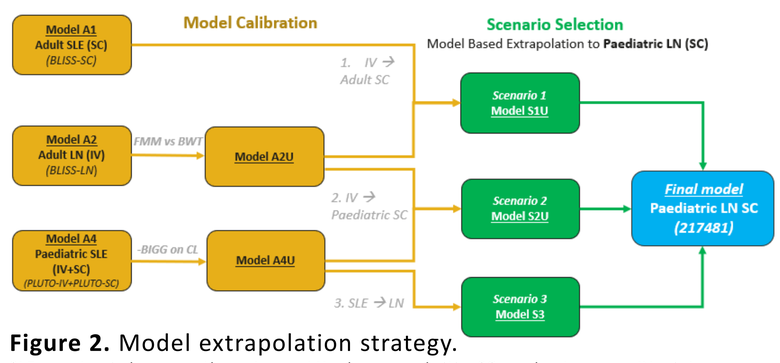

Figure 2. Model extrapolation strategy.
SLE = systemic lupus erythematosus, LN = lupus nephritis, SC = subcutaneous, IV = intravenous, FFM = baseline fat-free body mass; BIGG = baseline IGG, BWT = baseline body weight.

1. *Model Calibration:*
1. Covariate selection.
2. Allometric scaling parameters.

2. *Scenario selection:*
3. SC from adult or paediatric SLE model.
4. Systemic parameters from adult LN or paediatric SLE.

Results

A. Final fit-for-purpose population PK model (adult LN IV with paediatric SC, S2U)

Parameter	Implementation	Estimate (fixed)	Source model
F (fraction)	θ	0.703	Model A4 (E.mod)
ALAG (day)	θ	0.179	Model A4 (E.mod)
Kabs (1/day)	θ	0.287	Model A4 (E.mod)
CL (mL/day)	θ	175	Model A2 (A.mod)
V1 (mL)	θ	2728	Model A2 (A.mod)
Q (mL/day)	θ	487	Model A2 (A.mod)
V2 (mL)	θ	1992	Model A2 (A.mod)
Covariates			
Body size on CL	$(BWT/60)^{\theta}$	0.526	Model A2U (C.mod)
Body size on V1	$(BWT/60)^{\theta}$	0.604	Model A2U (C.mod)
Body size on Q	$(BWT/60)^{\theta}$	0.526	Model A2U (C.mod)
Body size on V2	$(BWT/60)^{\theta}$	0.604	Model A2U (C.mod)
ALB on CL	$(ALB/42)^{\theta_1/(1+\theta_2 \cdot PROT)}$	-1.74	Model A2 (A.mod)
PROT on ALB		0.0832	Model A2 (A.mod)
PROT on CL	$1 + \theta \cdot PROT$	0.0663	Model A2 (A.mod)
IIV			
CL	ω^2	0.0593	Model A2 (A.mod)
V1	ω^2	0.0322	Model A2 (A.mod)
V2	ω^2	0.133	Model A2 (A.mod)
Prop	ω^2	0.346	Model A2 (A.mod)
Residual variability			
Proportional	σ^2	0.240	Model A2U (C.mod)
Additive	σ^2	0.1	Model A2 (A.mod)

Table 2. Parameter estimates from the final population PK model.

- The calibrated **adult LN IV model** (A4U) was used as the **base model:**
  - BWT scaling replaced FFM on CL, V1, Q, and V2:
    - Scaling parameters were re-estimated on adult LN IV data
  - Time-dependent LN covariates from adult LN IV model
- **SC absorption parameter** estimates were taken from the **ped SLE SC model** (A4)

B. Model Part-Validations

- The model constructed for a paediatric LN SC population predicted paediatric SLE exposures well.
- The LN related covariates (albumin and proteinuria) are similarly distributed between adult and paediatric patients, supporting the extrapolation of adult LN parameters to a paediatric population.

C. Simulation

The final population PK model was used to perform simulations to select the appropriate SC dosing regimen, including loading dose, in paediatric LN patients. The **2-weight band regimen** was chosen**:**

- **≥15-<40 kg:** 200 mg SC weekly (QW) for the first 4 doses, followed by 200 mg SC every two weeks thereafter.
- **≥40 kg:** 400 mg SC QW for the first 4 doses, followed by 200 mg SC QW thereafter.

Weight band regimen	Weight category	Loading schedule *Week 0-4*	Maintenance schedule *>Week 4*
2-weight band regimen	<40 kg	200 mg QW	200 mg Q2W
	≥40 kg	400 mg QW	200 mg QW
Main 3-weight band regimen	<30 kg	200 mg QW	200 mg Q2W
	≥30-<50 kg	200 mg QW	200 mg Q10d
	≥50 kg	400 mg QW	200 mg QW
Alternative 3-weight band regimen	<30 kg	200 mg QW	200 mg Q2W
	≥30-<50 kg	400 mg Q10d[a]	200 mg Q10d
	≥50 kg	400 mg QW	200 mg QW

[a]3 doses of 200 mg Q10d are administered during a loading period of 30 days rather than 28 days.

Table 3. Simulated weight band regimens.

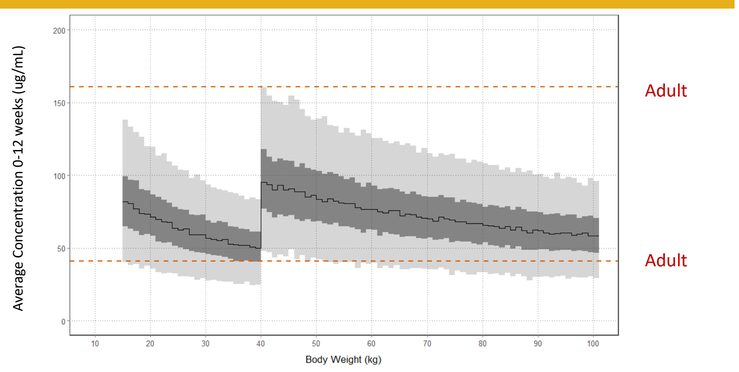

Figure 3. Simulated Cavg (Wk 0-12) over Body Weight in Paediatric LN Patients (5-17 years) in Simulated 1 Kg Weight Groups (N=1000/group).
Black solid line: median, dark shaded region: inter-quartile range, light shaded region: 95% prediction interval. Dashed red lines: 2.5 and 97.5 percentiles of Cavg (Wk 0-12) in the adult LN IV patients at 41 and 161 µg/mL, respectively.

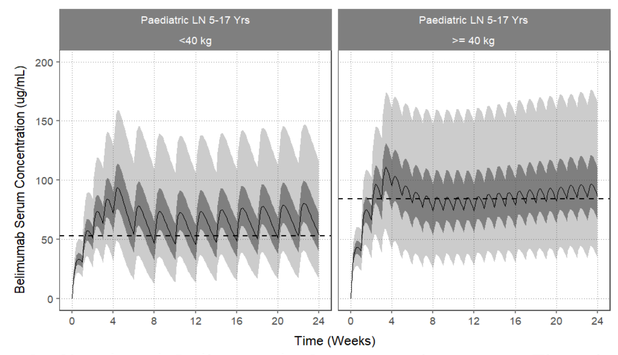

Figure 4. Simulated Belimumab Concentrations over Time in a Virtual Population of Paediatric LN Patients per Weight Band.
Black solid line: median, dark shaded region: inter-quartile range, light shaded region: 95% prediction interval, black dashed line: trough concentration at 24 weeks.

Conclusions

Simulations based on an extrapolated, fit-for-purpose, population PK model enabled the selection of an appropriate dosing regimen, the **2-weight band regimen**, for belimumab SC administration in paediatric LN patients.

The 2-weight band regimen resulted in exposures that met the following requirements:

1. Good **balance** between exposure and practical dosing regimen.
2. **Convenient** for patients and caregivers and does not include 10-day dosing schedule of the 3-weight band regimens.
3. **Early exposures** (Cavg(Wk 0-12)) were consistent across the paediatric weight range and similar to those in adult LN for which safety and efficacy has been established.
4. The **loading period** established approximated steady state concentrations that were achieved early, i.e. within 4 weeks of starting treatment.
5. The **simulated steady state** (approximated at week 24) exposures in paediatric LN patients **were similar to the simulated adult LN** and to simulated ped SLE SC steady state exposures.

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Disclosures
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